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A review for natural polysaccharides with anti-pulmonary fibrosis properties, which may benefit to patients infected by 2019-nCoV

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ABSTRACT

Pulmonary fibrosis (PF) is a lung disease with highly heterogeneous and mortality rate, but its therapeutic options are now still limited. Corona virus disease 2019 (COVID-19) has been characterized by WHO as a pandemic, and the global number of confirmed COVID-19 cases has been more than 8.0 million. It is strongly supported for that PF should be one of the major complications in COVID-19 patients by the evidences of epidemiology, viral immunology and current clinical researches. The anti-PF properties of naturally occurring polysaccharides have attracted increasing attention in last two decades, but is still lack of a comprehensively understanding. In present review, the resources, structural features, anti-PF activities, and underlying mechanisms of these polysaccharides are summarized and analyzed, which was expected to provide a scientific evidence supporting the application of polysaccharides for preventing or treating PF in COVID-19 patients.

1. Introduction

Pulmonary fibrosis (PF) is a worldwide disease, along with progressive and permanent fibrotic "scar" in alveolus and bronchioles of the lung parenchyma (Jacob et al., 2018), which could be induced by genetic susceptibility and various environmental risk factors including virus, bacteria, cigarette smoke, wood dust, stone dust *etc.* (Martinez et al., 2017; Richeldi, Collard, & Jones, 2017). Interana and pirfenidone were approved by the USA Food and Drug Administration for suppressing the progression of pulmonary fibrosis (Raghu et al., 2015). In clinical, glucocorticoid (Ozaki et al., 1982), prednisone (Bickerman, Beck, & Barach, 1955), cyclophosphamide (Miniati & Cerinic, 2007), and other immunosuppressive modulators have also been used for delaying the degree of pulmonary fibrosis and prolonging the survival of patients. However, all of them cannot improve the risks of incidence and mortality of pulmonary fibrosis (Canestaro, Forrester, Raghu, Ho, & Devine, 2016), but cause a large economic burden for patient (Raimundo et al., 2016). Therefore, it is still urgent developing new therapies and drugs for treating pulmonary fibrosis.

The transformation of epithelial into myofibroblasts and the amount of extracellular matrix (ECM) generated by fibroblasts are considered as crucial developmental milestones in pulmonary, wherein a pivotal fibrogenic cytokine TGF-β is aberrantly expressed, which in turn triggers epithelial-mesenchymal transition (EMT) process thereby enhancing ECM deposition mediated by both Smad dependent and independent pathways (Bale, Venkatesh, Sunkoju, & Godugu, 2018; Liu, Lu, Kang, Wang, & Wang, 2017). Furthermore, some other mechanisms have been also found to be imperative in pulmonary fibrosis progression including inflammation, oxidative stress, deregulated ECM and EMT signaling (Liu et al., 2017).

Human coronaviruses were first described in the 1960s for patients with the common cold, which in the past two decades have caused severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), as well as COVID-19 now. A typical clinical feature

Abbreviations: ASP, total polysaccharides from *Angelica sinensis*; AUF1, an adaptor protein AU-binding factor 1; BALF, bronchoalveolar lavage fluid; BLM, bleomycin; BMSCs, bone marrow mesenchymal stem cells; COVID-2019, Coronavirus disease-2019; DANCR, differentiation antagonizing non-protein coding RNA; DOP, a neutral heteropolysaccharides from *Dendrobium officinale*; EMT, epithelial-mesenchymal transition; FMP-1, a polysaccharide from *Morchella esculenta*; FN, Fibronectin; HEPF cell, human embryo pulmonary fibrosis cell; IFN-γ, Interferon gamma; IL, Interleukin; IL-1RA, interleukin-1 receptor antagonist; LMWF, Low-molecular weight fucoidan; MCP-1, Monocyte chemotactic protein 1; MDA, malondialdehyde; MS80, a novel sulfated oligosaccharide extracted from seaweed; Mw, molecular weight; Nrf2, nuclear factor-erythroid 2-related factor 2; POL, Total polysaccharide from *O. lanpingensis*; OSM, Oncostatin M; FYGL-1, a neutral heteropolysaccharide from *G. lucidum*; PF, Pulmonary fibrosis; RLE-6TN cell, alveolar type II epithelial cell; ROS, reactive oxygen species; α-SMA, α-smooth muscle actin; SOD, superoxide dismutase; TGF-β1, transforming growth factor β1; TNF-α, Tumor necrosis factor-α

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associated with SARS is pulmonary fibrosis, which resulted in a high mortality and a low quality of life for recovered patients (Venkataraman & Frieman, 2017). Several long-term follow-up studies have demonstrated that more than 20 % of SARS survivors exhibited radiographic evidence of lung fibrotic changes (Hui et al., 2005; Xie et al., 2005). Recently, a retrospective analysis on the pulmonary computed tomographic imaging of fifty patients with COVID-19 pneumonia also observed the formation of fibrotic stripes during their rehabilitation period (Xu et al., 2020). It will be a high probability that pulmonary fibrosis is one of the major complications in COVID-19 patients. Therefore, there will be a huge need for effective and safety agents and therapeutic strategies for treating pulmonary fibrosis induced by COVID-19 (Wang et al., 2020).

With the broad spectrum of bioactivities and highly safety, polysaccharides have attracted more and more attention (Muhama, Zulkifli, Selvakumaran, & Lazim, 2019; Shi, 2016). In addition, several natural polysaccharides, such as polysaccharides-K (PSK) and polysaccharides-peptide (PSP) from *Coriolus versicolor* (Kidd, 2000), and fucoidan (Wang, Geng, Yue, & Zhang, 2019), have been applied in clinical for treating diseases and improving health. In fact, many studies have been conducted to reveal the anti-pulmonary fibrosis activities and underlying mechanisms of naturally occurring polysaccharides from medicinal plants, seaweed, and edible fungi. However, to the best of our knowledge, a comprehensively understanding of these anti-pulmonary fibrosis natural polysaccharides is still limited.

Thus, in present review, the available information about these natural polysaccharides with anti-pulmonary fibrosis activities were collected by searching in the related topics of “pulmonary fibrosis” and “polysaccharides” in the databases of Scopus (http://www.scopus.com) and China National Knowledge Infrastructure (https://www.cnki.net). In addition, the resources, structural features, physiological activities, as well as underlying mechanisms of these polysaccharides were systematically summarized and analyzed, which was expected to provide a scientific evidence for the application of polysaccharides for preventing or treating pulmonary fibrosis in COVID-19 patients.

2. Mechanisms underlying the anti-pulmonary fibrosis activities of natural occurring polysaccharides

2.1. Transforming growth factor β1 (TGF-β1)-Smad2/3 axis

TGF-β1 overproduction has been recognized as the most relevant element related to the progress of pulmonary fibrosis, which plays a crucial role in the induction of EMT, and stimulates differentiation, proliferation and migration of immature fibroblasts, as well as induces phenotypic conversion of fibroblasts into myofibroblasts (Walton, Johnson, & Harrison, 2017). Smad2 and Smad3 are the main transcription factors for TGF-β1 signals, which are phosphorylated and translocated into the nucleus upon ligand binding (Fig. 1).

DOP is a neutral heteropolysaccharides isolated from *Dendrobium officinale*, which consisted of Man and Glc (in a mole ration of 5.9:1) with an average molecular weight (Mw) at about 1.78×10^5 Da, and had a partial structure of *O*-acetylated glucomannan with β-D-configuration in pyranose sugar forms (He et al., 2016). It has been demonstrated that DOP could significantly attenuate bleomycin (BLM)-induced up-regulation of TGF-β1 expression and Smad2/3 phosphorylation in the rat lung tissues, and further suppress the transformation of rat type II alveolar epithelial cells into myofibroblasts (Chen et al., 2018) (Fig. 1).

Ginsan, a polysaccharide isolated from the roots of *Panax ginseng* with an average Mw of 1.5×10^6 Da, composed mainly of Glc and Gal (over 90 %, w/w), and 5–8 % Man and Ara (Ahn et al., 2011; Lee et al., 1997). In mouse lung fibroblasts (NIH/3T3 cells) or human lung fibroblasts (IMR-90 and WI-38 cells), ginsan could significantly reduce the phosphorylation of Smad2 and Smad3 induced by TGF-β *via* inhibiting induction of R-Smads but not inhibitory Smads (Smad6 or Smad7). In addition, ginsan significantly reduced the phosphorylation of ERK and Akt induced by TGF-β, but did not affect the phosphorylation of either JNK or p38, which indicated that ginsan down-regulated both Smad-dependent and independent signaling pathways induced by TGF-β. Furthermore, ginsan could obviously reduce the increases in protein expression of TGF-β receptors (TβRI and TβRII), and block the decrease in protein expression of TβRIII, a known co-receptor of TβRII (Ahn et al., 2011) (Fig. 1).

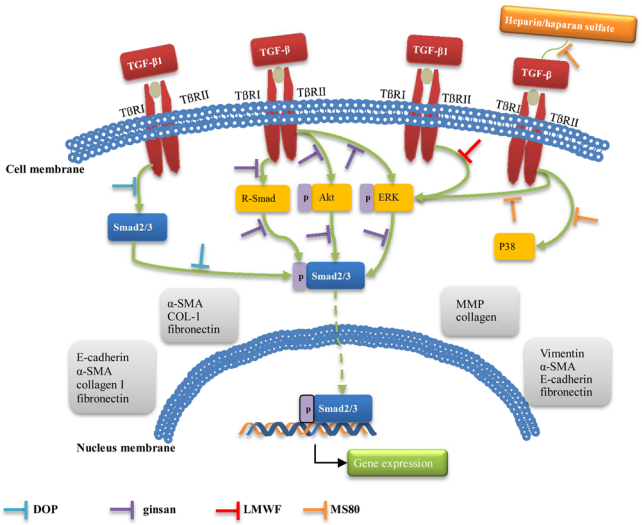

Fig. 1. Targeting TGF-β mediated Smad2/3 signaling for anti-pulmonary fibrosis effects of DOP, ginsan, LMWF and MS80.

ERK signaling is another important mechanism implicated in the process of TGF-β1induced EMT during the pulmonary fibrosis. Wang, Zhang et al. (2019) had demonstrated that a sulfated low-molecular weight fucoidan isolated from brown seaweed (LMWF) can ameliorate TGF-β1 induced EMT both *in vivo* and *in vitro* models of pulmonary fibrosis by downregulating ERK signaling, which significantly inhibited the over expression of TGF-β1 and p-ERK1/2 in mice induced by BLM, as well as suppressed the over expression of p-ERK1/2 in TGF-β1induced A549 cells (Fig. 1)

The high binding affinity for TGF-β1 have revealed to be closely related to the anti-pulmonary fibrosis activities of MS80, a marine-derived sulfated oligosaccharide (1→4 α-D-glucose) isolated from seaweed with the average Mw of 8×10^3 Da, which *via* competitively inhibiting the heparin/ HS-TGF-β1 interaction, can arrest TGF-β1-induced human embryonic pulmonary fibroblast (HEPF) cell proliferation, collagen deposition and matrix metalloproteinase activity, as well as deactivate both the ERK and p38 signaling pathways (Jiang & Guan, 2009).

2.2. DANCR/AUF-1/FOXO3 regulatory axis

The differentiation antagonizing non-protein coding RNA (DANCR) is a newly identified long noncoding RNA (lncRNA) with pivotal roles in cell proliferation, migration, invasion, and stem cell differentiation, which was shown to promote EMT progression and invasion capability of malignant cells (Yang, Sun, Gao, Meng, & Yang, 2018). DANCR cooperated with an adaptor protein AU-binding factor 1 (AUF1) has been demonstrated to regulate EMT and fibrogenesis by upregulating FOXO3 protein levels without influencing its mRNA expression. The root of *Angelica sinensis* is a well-known traditional Chinese medicine, which has been used for thousands of years to prevent and treat various diseases. The polysaccharides have been proved as one of the major effective ingredients in *A. sinensis*, and more than 30 polysaccharides have been identified from *A. sinensis*, most of which were heteropolysaccharides (Jin, Zhao, Huang, Xu, & Shang, 2012). Treatment with

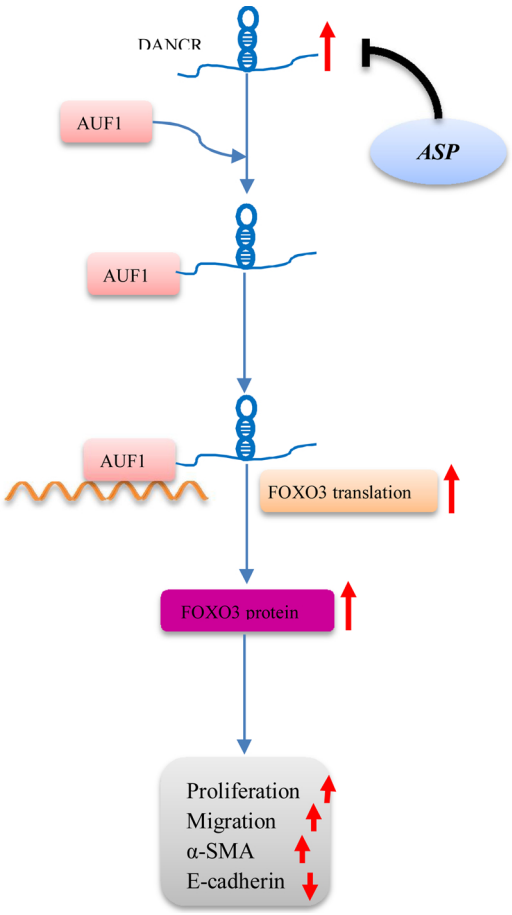

Fig. 2. Total polysaccharides from *A. sinensis* (ASP) suppress the pulmonary fibrosis *via* DANCR/AUF-1/FOXO3 regulatory axis.

total polysaccharide of *Angelica sinensis* (ASP) exhibited significant downregulatory effects on the expression of DANCR, which in turn represses AUF1-mediated FOXO3 translation to suppress the EMT and pulmonary fibrosis both in *in vitro* and *in vivo* (Qian, Cai, Qian, Wang, & Zhang, 2020) (Fig. 2).

2.3. Antioxidant ability

The pathological progresses of pulmonary fibrosis are complex, but oxidative stress injury plays an important role (Cameli et al., 2020). FYGL-1 is a neutral heteropolysaccharide isolated from *Ganoderma lucidum*, consisted of Gal, Rha and Glc (in a mole ration of 1.00:1.15:3.22) with an average Mw of 7.8×10^6 Da, and the backbone structure consisted mainly of 1,2-linked-β-LRha*p*, 1,3,6-linked-α-D-Gal*p*, 1,2,6-linked-α-D-Glc*p* and 1-linked-α-D-Glc*p* (Pan et al., 2012). Treatment with FYGL-1 (at 100 and 300 mg/kg for 28 days) led to a markedly reducing in the pulmonary index, inflammatory cell infiltration and collagen deposition in rats induced by BLM, which was associated with increased levels of glutathione, glutathione peroxidase, catalase and superoxide dismutase and decreased contents of malondialdehyde and hydroxyproline in the lung tissues (Chen et al., 2016).

2.4. Reducing the recruitment of macrophagesand neutrophil in the lung tissues

Pulmonary macrophages express several fibrotic mediators and play important roles in lung injury healing and fibrosis, which are currently classified into two phenotypes, classically activated macrophages (M1) with secretion of Th1-related cytokines (including TNF-α, IL-1β, and IL-6) and alternatively activated macrophages (M2) with release Th2-related cytokines such as IL-10 and IL-13. However, the migration and invasion ability of both M1 and M2 macrophages are promoted by monocyte chemotactic protein 1 (MCP-1), a chemokine mainly expresses in alveolar macrophages and participates in the chemotaxis of cells. Zhou et al. (2020) found that the total polysaccharides extracted from *Ophiocordyceps lanpingensis* (POL) could suppress the increasing level of MCP-1 expression during the process of BLM-induced pulmonary fibrosis, and consequently reduce the increased amount of M1 and M2 macrophages, as well as the expression levels of relative cytokines. Finally, the generation of myofibroblasts was alleviated based on the reduced expression of α-smooth muscle actin (α-SMA) protein (Fig. 3). According to Yu et al. (2018) studies, the increased expression of TIMP-1, CXCL1, MCP-1, MIP-2, and interleukin-1 receptor antagonist (IL-1RA) were strongly associated with radiotherapy-induced lung fibrosis through the induction of M2 macrophages and neutrophils. However, the administration of fucoidan isolated from *Sargassum hemiphyllum* (FSH) in irradiated mice significantly attenuated these cytokines expression in the collected pleural fluid and reduced pleural fluid-induced collagen expression in fibroblasts, which were correlated with the reduction of neutrophil and macrophage infiltration in lung tissues (Fig. 3).

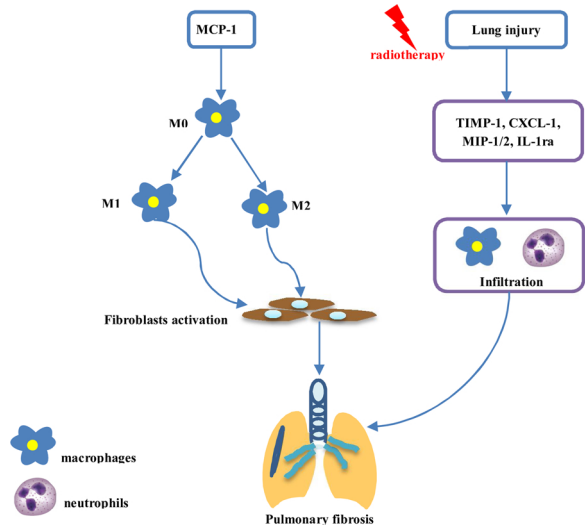

Fig. 3. Natural polysaccharides suppressed pulmonary fibrosis *via* reducing the recruitment of macrophages and neutrophils in the lung tissues.

3. The alleviating effects of naturally occurring polysaccharides on pulmonary fibrosis

3.1. Polysaccharides from plants

In present review, nine kinds of polysaccharides from plants were collected. The resources, structural features, and anti-pulmonary fibrosis activities of these polysaccharides were displayed in Table 1.

The root of *A. sinensis* is a well-known traditional Chinese medicine, which has been used for thousands of years to prevent and treat various diseases. The polysaccharides have been proved as one of the major effective ingredients in *A. sinensis*, and more than 30 kinds of polysaccharides have been identified from *A. sinensis*, most of which were heteropolysaccharides (Jin et al., 2012). Recently, Qian et al. (2020) have demonstrated that treatment with total polysaccharides from *A. sinensis* (ASP) significantly reversed BLM-induced collagen deposition and restored collagen-1 levels in lung tissue of SD rat. In addition, ASP treatment dramatically suppressed the increase growth rate and migratory ability of alveolar type II epithelial (RLE-6TN) cell stimulated by TGF-β1, and further abrogated TGF-β1-induced upregulation of α-

Table 1
The sources, structural characterization and anti-pulmonary fibrosis activities of natural polysaccharides from plants.

Name/source	Structural characterization	Experimental model	Effects	Reference
ASP/*A. sinensis*	Mw: 5.1 − 740 kDa; Containing Glc, Gal, GalA, Ara, Rha, Man, Fuc, Xyl; Linkage: backbone →4)-α-D-Glc*p*-(1→ with α-1,6-D-Glc*p*, β-L-Ara*f* residues at a branching position of O-6; backbone →3/6)-α-D-Glc*p*-(1→;backbone→4)-α-D-Gal*p*A-(1→2)-α-L-Rha*p*-(1→ with β-1,6- and β-1,4-Gal*p* and α-1,5-Ara*f* at a branching position of O-4; backbone→4)-α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→.	*In vivo*: BLM-induced Sprague-Dawley rats; *In vitro*: TGF-β1 induced alveolar type II epithelial (RLE-6TN) cells.	*In vivo*, ASP administration suppressed the increasing of collagen deposition accompanying with restoring collagen-1 protein levels by inhibiting the DANCR/AUF1/FOXO3 pathway in BLM-induced PF model rats. *In vitro*, ASP restored intercellular junction and spindle-like structure with downregulation of growth rate, migratory ability and α-SMA expression and upregulation of E-cadherin in RLE-6TN cells with TGF-β1 treatment.	Jin et al. (2012), Luo et al. (2017), Qian et al. (2020)
RAP/*Astragali radix*	Mw: 5.6 ~ 7600 kDa; Containing Glc, Rha, Gala, Ara, Xyl, Man, GlcA, Gala; Linkage: backbone 1,2,4-Rha*p*, α-1,4-Glc*p*, α-1,4-GalA*p*6Me, β-1,3,6-Gal*p* with 1,2,4-Rha*p*, β-1,3,6-Gal*p*, α-T-Ara*f*, α-1,5-Ara*f* at branching positions of O-4/O-2/O-3.	*In vivo*: BLM-induced Wistar rats;	*In vivo Astragalus* polysaccharides administration inhibited inflammation of pulmonary alveoli and upregulated the serum level of IFN-γ with downregulated the serum levels of IL-4 and TNF-α in BLM-induced PF model rats.	Li et al. (2011), Yin et al. (2012)
PBS/*B. striata*	Mw: 401.3 kDa;Containing Man and Glc.	*In vivo*: BLM-induced adult male Sprague Dawley rats;	*In vivo*, administration of PBS improved pulmonary histomorphology and histopathology with inhibiting collagen deposition, decreased pulmonary index and hydroxyproline contents in BLM-induced PF model rats.	Guo et al. (2016)
DOP/*D. officinale*	Mw: 178 kDa; Containing Man and Glc (5.9:1); Linkage: acetylated glucomannan with β-D configuration in pyranose.	*In vivo*: BLM-induced adult male Sprague Dawley rats; *In vitro*: TGF-β1 induced rat type II alveolar epithelial cells.	After DOP administration in BLM-induced PF model rats, the pulmonary index, hydroxyproline expression and serum TGFβ1 concentrations were lower, with the improvement of histopathology, morphology and the inhibition of neutrophil-dominant inflammation, expression on mRNA and protein of TGFβ1, Smad2, Smad3 and α-SMA protein expression. *In vitro*, DOP decreased the expression of α-SMA, Smad 2/3 protein, pSmad 2/3 protein and the synthesis of collagen 1 and fibronectin with increasing the expression of E-cadherin.	Chen et al. (2018), He et al. (2016)
BHP-1/*L. davidii var. unicolor*	Mw: 1.93 × 10^5 Da; consisted of Glc and Man in a relative molar ration of 5.9: 2.0; Backbone: mainly contained α-1,4-linked D-Glc*p* and β-1,4-linked D-Man*p*: the branches were probably linked at the *O*-2 and or O-3 of the Man and Glc residues, with *T*-*α*-D-Glc*p* as a terminal structure	*In vivo*: BLM-induced SPF Kunming mice.	Combined with bone marrow mesenchymal stem cells transplantation, BHP-1 decreased the pulmonary index and improved the pulmonary histopathology and collagen deposition with downregulating the protein expression of TNF-α and NF-κB in BLM-induced PF model mice.	Luo et al. (2013), Hui et al. (2019), Hu et al. (2019)
TPOB/*O. basilicum*	Containing Glc, Xyl, Gal; Linkage: backbone β-D-Glc*p* with α-D-Xyl*p*; β- D-Gal*p*-(1→2)-α-D-Xyl*p* at a branching position of O-6.	*In vitro*: TGF-β1 induced human A549 cells.	*In vitro*, TPOB changed less in morphology and reduced hydroxyproline contents with upregulating the expression levels of E-cadherin and downregulating the expression levels of Vimenth, α-SMA and COL1 in humanA549 cells with TGF-β1 treatment.	Hoffman et al. (2005), Yan et al. (2017)
Ginsan/*P. ginseng* C.A. Meyer	Mw: 3.5 ~ 160 kDa; Containing Glc, Gal, Man, Ara; Linkage: backbone →5)-α-L-Ara*p*-(1, →3)-α-D-Gal*p*-(1→ with α-3,5-L-Ara; β-1,4-D-Gal at branching positions ofO-3/O-4 /O-6.	*In vivo*: BLM-induced male C57BL/6 mice; *In vitro*: TGF-β1 induced NIH/3T3 cells and IMR-90 and WI-38 cells	*In vivo*, Ginsan administration changed nothing in morphology and attenuated TGF-β expression in lung tissue with downregulating the levels of collagen and α-SMA in BLM-induced PF model mice. *In vitro*, Ginsan suppressed the expression of α-SMA, FN, procollagen type 1 and downregulated both Smad-dependent and -independent signaling pathways with modulates TGF-β receptor levels (downregulating the TβRI and TβRII protein	Ahn et al. (2011), Sun (2011)

(*continued on next page*)

Table 1 (*continued*)

Name/source	Structural characterization	Experimental model	Effects	Reference
			expression levels and upregulated the TβRIII protein expression level) in mouse and human lung fibroblasts with TGF-β1 treatment.	
TPRH/*Radix Hedysari*	Mw: 1.2 – 668 kDa; Containing Glc, Gal, Ara, Rha, Xyl, Gala, Man and some ester sulfate; Linkage: backbone →4)-α-D-Glcp-(1→ and→1)-α-D-Glcp-(6→1)-α-L-Rhap-(2→ with α-L-Araf, α-D-Glc, α-D-Gal at branching positions of O-4/ O-6; backbone →4)-β-D-Galp-(1→ and →4)-α-D-Glcp-(1→ with α-L-Araf, α-L-Rha*p*, α-D-Glc at a branching position of O-6; backbone →6)-α-D-Glcp-(1→ and →5)-α-L-Araf-(1→ with α-D-Glc, α-L-Araf-(1→2)-α-L-Rha*p*, α-L-Araf at branching positions of O-2/O-3.	*In vivo*: BLM-induced Wistar rats.	*In vivo*, TPRH administration improved pulmonary histopathological morphology, inflammation of pulmonary alveoli and proliferation and deposition of collagen fibrils with reducing the contents of hyaluronic acid and laminin in lung tissue of BLM-induced PF model rats. *In vivo* combined small dose prednisone, TPRH administration alleviated alveolar inflammation, fibrosis degree and histopathology changes with downregulating the expression levels of collagen and TGF-β1 in BLM-induced PF model rats.	Lei et al. (2008), Qiang, Wang, Li, Wang & Li (2018), Su et al. (2016)
RSA/*R. sachalinensis*	Ara, Rha, Xyl, Glc, Gal, and GalA in the mole ration of 1.00: 3.23: 0.26: 0.34: 0.84: 10.24	*In vitro*: TGF-β1 induced human lung carcinoma type II epithelial (A549) cells.	*In vitro*, RSA improved morphological change, inhibited cell mortality, increased cell livability and downregulated the expression of fibronectin-EDA (Fn-EDA) with the inhibition of transformation to ectomesenchymal cells in A549 cells with TGF-β1 treatment.	Han et al. (2002), Li et al. (2016)

SMA and downregulation of E-cadherin expression in RLE-6TN cells. The similar inhibitory effect of ASP was also observed in TGF-β1 induced HEPF cell assay, which showed that ASP (at 25 μg/mL) significantly reduced the elevated content of hydroxyproline and the upregulated protein expressions of α-SMA and CTGF (Luo et al., 2017).

Chen et al. (2018) have demonstrated that DOP (a neutral heteropolysaccharides isolated from *D. officinale*) treatment significantly ameliorated indices for both pulmonary inflammation and fibrosis in a BLM-induced pulmonary fibrosis model in rats, which can significantly lower BLM-induced elevations of pulmonary index, total cell numbers and differential neutrophil counts in bronchoalveolar lavage fluid (BALF), as well as attenuate the average scores of BLM-induced histopathological changes, and decrease the BLM-induced increase in hydroxyproline content in lung tissue. A polysaccharide isolated from rhizome of *Bletilla striata* (PBS), with an average Mw of 4.01×10^5 Da and mainly consisted of Man and Glc, also exhibited the similar anti-pulmonary fibrosis activities in BLM-induced SD rat model, which obviously improved the BLM-induced histopathological changes of lung tissues and significantly lowered the pulmonary index and hydroxyproline content (Guo et al., 2016). In addition, the PBS did not cause any side-effect *in vivo* with oral administration of 4000 mg/kg/day (He et al., 2017).

RAP was a water-soluble polysaccharide purified from *Radix astragali* and composed of Rha, Ara, Glc, Gal, and GalA in a mole ratio of 0.03: 1.00: 0.27: 0.36:0.30 with an average Mw at 1.3×10^5 Da. The backbone of RAP consisted of 1,2,4-linked Rha*p*, α-1,4-linked Glc*p*, α-1,4-linked GalA*p*, β-1,3,6-linked Gal*p*, with branched at *O*-4 of the 1,2,4-linked Rha*p*, and *O*-3 or *O*-4 of β-1,3,6-linked Gal*p*, while the side chains mainly consisted of α-T-Ara*f* and α-1,5-linked Ara*f* with *O*-3 as branching points and trace Glc and Gal (Yin et al., 2012). The potential inhibitory effects of RAP against BLM-induced pulmonary fibrosis had been demonstrated in a Wistar rats model, which significantly inhibited the alveolar inflammation, downregulated the serum levels of interleukin-4 (IL-4) and tumor necrosis factor-α (TNF-α), but upregulated the serum level of interferon gamma(IFN-γ) (Li et al., 2011).

A total polysaccharides (TPRH) was isolated and purified from *Radix hedysari*, mainly composed of Ara, Man, Gal and Glc in a mole ratio of 0.42: 0.53: 0.34: 1.00, with an average Mw of 1.9×10^5 Da, and the purity of which was 94.3 % (Lei, Zhao, Wang, Yao, & Ding, 2008). Treatment with TPRH (200 mg/kg), combined with prednisone (3 mg/kg), exhibited a significant inhibitory effect against alveolar inflammation in BLM-induced Wistar rat pulmonary fibrosis, and further alleviated fibrosis degree, histopathology changes, as well as the expression levels of collagen and TGF-β1 with reducing the contents of hyaluronic acid and laminin in lung tissues of rats exposed to BLM (Lei et al., 2008). Meanwhile, TPRH demonstrated to possess the similar ameliorate effects on pulmonary histopathological morphology, inflammation of pulmonary alveoli and proliferation and deposition of collagen fibrils with reducing the contents of hyaluronic acid and laminin in lung tissue of BLM-induced pulmonary fibrosis model rats (Su et al., 2016).

In both BLM-induced C57BL/6 mice and TGF-β1-induced murine and human normal lung fibroblasts models, ginsan (a polysaccharide isolated from the roots of *P. ginseng*) exhibited the significant inhibitory effects against pulmonary fibrosis, which changed nothing in morphology, attenuated TGF-β expression, and reduced the levels of collagen and α-SMA in lung tissues, as well as suppressed the expression of α-SMA, fibronectin (FN) and collagen type 1 (Ahn et al., 2011). In addition, administration of ginsan (6 g/day) showed no significant adverse effect in a 14-week randomized, placebo-controlled, double-blind clinical trial (Cho, Son, & Kim, 2014).

BHP-1, a polysaccharide isolated from the bulbs of *Lilium davidii* var. *unicolor*, was mainly consisted of Glc and Man in a mole ration of 5.9: 2.0, with the average Mw of 1.93×10^6 Da. The backbone of BHP-1 mainly contained α-1,4-linked D-Glc*p* and β-1,4-linked D-Man*p*, and the branches were probably linked at the *O*-2 and or O-3 of the Man and Glc

Table 2
The sources, structural characterization and anti-pulmonary fibrosis activities of natural polysaccharides from seaweeds.

Source/name	Structural characterization	Experimental model	Effects	Reference
L. japonica/ LMWF	Mw: 8 − 10 kDa; Containing Rha, Fuc, Xly, Man, Glc, Gal, GlcA, Gala; Linkage: backbone →3)-Galp-(1→, →6)-Glcp-(1→, →6)-Galp-(1→, →3,6)-manp-(1→ with →3)-Fucp-(1→, →4)-Glcp-(1→ and sulfated end units.	*In vivo*: BLM-induced male C57BL/6 mice; *In vitro*: TGF-β1 induced A549 cells.	After LMWF administration in BLM-induced PF model mice, lung fibrotic histopathology and lung hydroxyproline content was significantly improved, levels of TGF-β1 expression (in BALF and lung tissue) and the lung EMT phenotype (the expression trends of E-cadherin, α-SMA and fibronectin) was attenuated, as well as ERK signaling was downregulated. *In vitro* TGF-β1-induced A549 cells, LMWF significantly inhibited the cell morphologic alterations and proliferation, attenuated EMT phenotype (less expression of E-cadherin and over expression of vimentin, α-SMA and fibronectin mRNA), and downregulated the over expression of p-ERK1/2 induced by TGF-β1.	Cui et al. (2016), Wang et al. (2019)
S. hemiphyllum/ FSH	Mw: 0.8 kDa; Containing rich L-fucose and sulfated ester groups with some D-xylose, D-galactose, D-mannose, glucuronic acid and a mixture of fatty acid methyl esters.	*In vivo*: radiotherapy (10 Gy/shot)-induced pneumonitis and lung fibrosis in C57BL/6 mice.	Fucoidan administration attenuated the increasing of pro-collagen 1α deposition, neutrophil (over expression levels of Ly6G mRNA) and macrophages (over expression levels of F4/80 mRNA) infiltration in lung tissues, reduced cytokine expression (TIMP-1, CXCL1, MCP-1, MIP-2, IL-1Ra, TREM-1, SDF-1/CXCL12 and IL-16) in the pleural fluid induced by radiation in mice.	Yu et al. (2018), Zheng, Li, Liu, Yuan & Lu (2001)
A kind of seaweed/ MS80	Mw: 8 kDa; Backbone →4)-α-D-Glcp-(1→ with sulfated residues and hydroxymethylated group.	*In vivo*: BLM-induced pathogen-free adult Wistar rats; *In vitro*: TGF-β1 induced HEPF cells.	After MS80 administration in BLM-induced PF model rats, there were some improvements in morphology and increasing hydroxyproline content of lung tissue. *In vitro*, MS80 inhibited the combining capacity of TGF-β1 with heparin examined by surface plasm on resonance and the proliferation, collagen deposition and matrix metalloproteinase activity of HEPF cells with TGF-β1 or BALF.	Jiang & Guan (2009)

residues, with *T*-α-D-Glc*p* as a terminal structure (Hu et al., 2019; Hui et al., 2019). Administration of BHP-1 with or without bone marrow mesenchymal stem cells (BMSCs) transplantation could significantly reduce the pulmonary index, improve the pulmonary histopathology and collagen deposition, and downregulate the protein expression of TNF-α and NF-κB in lung tissues of Kunming mice exposed to BLM. In addition, the effects of combined intervention are better than that of BHP-1 or BMSCs transplantation alone (Luo et al., 2013).

Total polysaccharides from *Ocimum basilicum* (TPOB) mainly consisted of Man, Rha, Glc, Fru and Ara (the mole ratio of these monosaccharides was not reported) with an average Mw of $8-10 \times 10^4$ Da (Zhan, An, Wang, Sun, & Zhou, 2020). TPOB showed the potential suppression of pulmonary fibrosis in TGF-β1-induced human A549 cells, with improving morphological change and reduction in hydroxyproline contents, upregulating the expression levels of E-cadherin and downregulating the expression levels of Vimentin, α-SMA, type I collagen and fibronectin-EDA (Fn-EDA) (Yan et al., 2017). RSA, an acidic heteropolysaccharide isolated from *Rhodiola sachalinensis*, was mainly consisted of Ara, Rha, Xyl, Glc, Gal, and GalA in a mole ration of 1.00: 3.23: 0.26: 0.34: 0.84: 10.24, which showed a potential suppression of pulmonary fibrosis in TGF-β1-induced human A549 cells, with improving morphological change and reduction in hydroxyproline contents, upregulating the expression levels of E-cadherin and downregulating the expression levels of Vimenth, α-SMA, COL-1 and fibronectin-EDA (Fn-EDA) (Han et al., 2002; Li, Gao, Zhao, & Hong, 2016).

In addition, the crude polysaccharides from three different complex prescriptions of Traditional Chinese Medicine (Fei Kang Ling, Gua Lou Xie Bai decoction, and Yu Ping Feng) also exhibited potential anti-pulmonary fibrosis activities in different *in vitro* and *in vivo* assays (Gao, 2016; Jiang, 2008; Xu et al., 2014).

3.2. Polysaccharides from algae

MS80 is a marine-derived sulfated oligosaccharide (1→4 α-D-glucose) isolated from seaweed with the average Mw at 8×10^3 Da. MS80 showed a significant inhibitory effect against pulmonary fibrosis induced by BLM in Wistar rats without toxicity, with improving pathological settings and decreasing lung collagen contents through competitively inhibition of heparin/heparan sulfate-TGF-β1 interaction (Jiang & Guan, 2009). In addition, MS80 could arrest TGF-β1-induced HEPF cell proliferation, collagen deposition and matrix metalloproteinase activity (Jiang & Guan, 2009) (Table 2).

LMWF, another sulfated polysaccharide extracted from brown seaweed, has also demonstrated to possess a significant inhibition of BLM-induced pulmonary fibrosis in C57BL/6 mice, as evidenced by improved lung histopathology and hydroxyproline content, attenuated the expression levels of TGF-β1 in BALF and lung tissue, and the lung EMT phenotype including the expression trends of E-cadherin, α-SMA and fibronectin (Wang et al., 2019) (Table 2). Furthermore, LMWF displayed no mutagenicity by either the bacterial reverse mutation or chromosomal aberration assays *in vitro* (at 5000 μg/mL), as well as no toxicological indications *in vivo* by repeated oral administration of LMWF (2000 mg/kg/day) for 28 days (Hwang, Yan, Lin, Li, & Lin, 2016). In addition, LMWF could significantly inhibited the morphologic alterations and proliferation of A549 cells induced by TGF-β1, and attenuated TGF-β1-induced EMT phenotype such as less expression of E-cadherin and over expression of vimentin, α-SMA and fibronectin (Wang et al., 2019).

The inhibitory effects of FSH has been reported against radiation pneumonitis and relative lung fibrosis in C57BL/6 mice treated by irradiated (10 Gy/shot) (Yu et al., 2018), which indicated that administration of FSH significantly attenuated the increasing in pro-collagen 1α deposition, neutrophil (over expression levels of Ly6G mRNA) and macrophages (over expression levels of F4/80 mRNA) infiltration in lung tissues, and reduced cytokine expression (TIMP-1, CXCL1, MCP-1,

Table 3
The sources, structural characterization and anti-pulmonary fibrosis activities of natural polysaccharides from fungi.

Name/source/	Structural characterization	Experimental model	Effects	Reference
Cordyceps	Mw: 2×10^5 Da	*In vivo*: pingyangmycin-induced ICR mice.	*In vivo*, cordyceps polysaccharide increased the IL-1RA levels, decreased the hydroxyproline content and shrank the fibrosis area in pingyangmycin-induced PF model mice.	Hu et al. (2019)
FYGL-1/*G. lucidum*	Mw: 7.8×10^4 Da; consisted of Gal, Rha and Glc in a mole ratio of 1.00: 1.15: 3.22; backbone structure: 1,2-linked β-L-Rha*p*, 1,3,6-linked α-D-Gal*p*, 1,2,6-linked α-D-Glc*p* and 1-linked α- D-Glc*p*	*In vivo*: BLM-induced adult male Sprague-Dawley rats.	After FYGL-1 administration in BLM-induced PF model rats, the pulmonary index, inflammatory cell infiltration and collagen deposition reduced with upregulating the levels of glutathione, glutathione peroxidase, catalase, superoxide dismutase and downregulating the levels of malondialdehyde and hydroxyproline in the lung.	Chen et al. (2016), Pan et al. (2012)
FMP-1/*M. esculenta*	Mw: 4.7×10^3 Da; consisted of Man, Glc and Gal in a mole ratio of 1.00: 7.84: 1.24; backbone structure: →4)-α-D-Glc*p*-(1→,→6)-α- D-Gal*p*-(1→ with α-1,6-D-Glc*p*, α-1,4-D-Glc*p*, β-1,6-D-Man*p*at a branching position of O-6.	*In vitro*: H_2O_2-induced human alveolar epithelial cells (A549).	*In vitro*, FMP-1 increased the cell viability with attenuating LDH release, decreased the cell apoptosis with attenuating the release of Cytochrome c and caspase-3, downregulated the expression levels of ROS and MDA, upregulated the activities of SOD and T-AOC in A549 cells, underlying antioxidative effect with PI3K/AKT/Nrf2/HO-1 signaling pathway.	Cai et al. (2018), Li et al. (2018)
POL/*O. lanpingensis*[a]	Mw: 3.2×10^5 Da; Containing Gal, Man and Glc in a ratio of 5.30: 13.38: 81.31	*In vivo*: BLM-induced male mice (C57BL/6).	*In vivo*, POL improved histopathological changes, reduced collagen deposition and the accumulation of macrophages (inhibiting the expression levels of NOS2, CXCL10/IP10, MARCO and ST2), downregulated the expression levels of pro-inflammatory and pro-fibrogenic factors (TNF-α, IL-1β, IL-6, OSM,IL-10, IL-13, α-SMA, MCP-1 and TGF-β1) and inhibited MDA production with promoting SOD level in BLM-induced PF model mice.	Zhou et al. (2020)

MIP-2, IL-1RA, TREM-1, SDF-1/CXCL12 and IL-16) in the pleural fluid induced by radiation in mice (Table 2).

3.3. polysaccharides from fungi

Four kinds of natural polysaccharides from fungi were collected in the present review. The resources, structural features, and anti-pulmonary fibrosis activities of these polysaccharides were displayed in Table 3.

Polysaccharides from *Cordyceps* (polysaccharide content > 64 %, average Mw < 2×10^5 Da) exhibited a significant inhibition of pingyangmycin-induced pulmonary fibrosis in mice, which could increase the IL-1RA levels, and reduce the hydroxyproline content and fibrosis area (Hu, Yang, Bai, & Fu, 2019). FYGL-1, a neutral heteropolysaccharide isolated from *G. lucidum*, showed the similar inhibitory effect on BLM-induced pulmonary fibrosis in rats, which could suppress the pulmonary index, inflammatory cell infiltration and collagen deposition, as well as ameliorate the oxidative stress in the lung tissue, such as upregulating the levels of glutathione, glutathione peroxidase, catalase, superoxide dismutase (SOD) and downregulating the levels of malondialdehyde (MDA) (Chen et al., 2016).

POL is a homogeneous polysaccharide isolated from *O. lanpingensis*, primarily composed of Gal, Man and Glc in the mole ration of 5.30: 13.38: 81.31, with an average Mw of 3.2×10^5 Da (Zhou et al., 2020). POL could improve histopathological changes, collagen deposition and the accumulation of macrophages (*via* inhibiting the expression levels of NOS2, CXCL10/IP10, MARCO and ST2), downregulate the expression levels of pro-inflammatory and pro-fibrogenic factors including TNF-α, IL-1β, IL-6, OSM, IL-10, IL-13, α-SMA, MCP-1 and TGF-β1, as well as inhibit oxidative stress (such as MDA production and SOD level) in BLM-induced pulmonary fibrosis mice (Zhou et al., 2020).

FMP-1 is a heteropolysaccharide from the fruiting bodies of *Morchella esculenta*, which has an average Mw of 4.7×10^3 Da and consisted of Man, Glc and Gal (in a mole ratio of 1.00:7.84:1.24), with the backbone made up of 1,4-linked Glc*p* and 1,6-linked Gal*p* (Cai et al., 2018). At the doses of 0 − 300 μg/mL, FMP-1 exhibited a potential anti-pulmonary fibrosis activity in H_2O_2-induced human alveolar epithelial A549 cells, without no inhibitory effect on cells' proliferation, which could attenuate H_2O_2-induced cytochrome c and Caspase-3 release to prevent cell apoptosis *via* inhibition of MDA and ROS levels, and enhancement the enzymatic activities of SOD and total antioxidant capacity (Li et al., 2018). In addition, the high degree of branching, low molecular weight and favorable structures (*e.g.* 1,4-linked Glc*p*, 1,6-linked Gal*p* and 1.6-linked Man*p*) are supposed to play an essential role in excellent antioxidant activities (Cai et al., 2018).

4. Conclusion

In present review, the structural features, physiological activities, and underlying mechanisms of 16 kinds of natural polysaccharides from plant, algae and fungi were systematically summarized and analyzed. The anti-pulmonary fibrosis activities of natural polysaccharides such as ASP, BHP-1, ginsan, TPRH, MS80, LMWF, and FYGL-1, have been demonstrated in different *in vivo* and *in vitro* assays, which can significantly ameliorate the pulmonary index, histopathological changes, and collagen deposition in rats or mice induced by BLM. And the main mechanisms of the anti-pulmonary fibrosis activities of these polysaccharides were targeting the TGF-β/Smad2/3 and DANCER/AUF-1/FOXO3 regulatory axis, and reducing the recruitment of macrophages and neutrophil. Furthermore, the sources of these polysaccharides are most edible materials, and the safety of ginsan, PBS and LMWF have been demonstrated in different *in vivo* and *in vitro* assays. Therefore, these polysaccharides maybe considerate as the safety and effective alternative agents for preventing or treating pulmonary fibrosis in COVID-19 patients.

Compliance with ethical standards

The authors declare that they have no conflict of interests.

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