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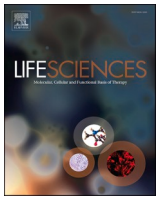

Investigating the possible mechanisms of pirfenidone to be targeted as a promising anti-inflammatory, anti-fibrotic, anti-oxidant, anti-apoptotic, anti-tumor, and/or anti-SARS-CoV-2

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ABSTRACT

Pirfenidone (PFD) is a non-peptide synthetic chemical that inhibits the production of transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), Interleukin 1 beta (IL-1β), and collagen 1 (COL1A1), all of which have been linked to the prevention or removal of excessive scar tissue deposition in many organs. PFD has been demonstrated to decrease apoptosis, downregulate angiotensin-converting enzyme (ACE) receptor expression, reduce inflammation through many routes, and alleviate oxidative stress in pneumocytes and other cells while protecting them from COVID-19 invasion and cytokine storm. Based on the mechanism of action of PFD and the known pathophysiology of COVID-19, it was recommended to treat COVID-19 patients. The use of PFD as a treatment for a range of disorders is currently being studied, with an emphasis on outcomes related to reduced inflammation and fibrogenesis. As a result, rather than exploring the molecule's chemical characteristics, this review focuses on innovative PFD efficacy data. Briefly, herein we tried to investigate, discuss, and illustrate the possible mechanisms of actions for PFD to be targeted as a promising anti-inflammatory, anti-fibrotic, anti-oxidant, anti-apoptotic, anti-tumor, and/or anti-SARS-CoV-2 candidate.

1. Introduction

Pirfenidone (PFD) (5-methyl-1-phenyl-2-[*1H*]-pyridone) is an orally active small molecule comprising a modified phenyl pyridine. It is an anti-fibrotic drug, commonly used for the treatment of idiopathic pulmonary fibrosis (IPF). PFD was firstly approved in Japan under the trade name Pirespa® and some years later in Europe, the United States, and Canada under the trade name Esbriet® (Roche Pharmaceuticals) for the same care. PFD has been reported to exert anti-inflammatory, antioxidant, and anti-fibrotic effects [1]. It has been shown to reduce the fibrosis of different organs; lung, kidney, liver, heart, and vascular remodeling. Also shows a significant anti-fibrotic effect in chronic kidney disease. Intraperitoneal and oral administration of PFD reduced the tissue levels of inflammatory markers [2]. The anti-fibrotic mechanism of PFD is associated with inhibition of both the production and activity of transforming growth -beta (TGF-β1) [3]. TGF-β1 is one of the major extracellular matrix (ECM) protein deposition regulators. Thus, blocking TGF-β1 pathways might be a pharmacological intervention in cardiac remodeling involving cardiac hypertrophy. Also, it suppressed collagen type 1 mRNA expression. TGF-β is an important cytokine that facilitates fibrosis. It induces alpha-smooth muscle actin (α-SMA), pro-collagen (Col)-I messenger RNA (mRNA), and protein levels, all of which are attenuated by PFD [4]. Also, TGF-β-induced phosphorylation of Smad3, p38, and a serine/threonine-specific protein kinase (AKT). Additionally, by inhibiting tumor necrosis factor-alpha (TNFα), fibroblast growth factor (FGF), interleukin-one beta (IL-1β), and by reducing platelet-derived growth factor (PDGF) and collagen, type one, alpha one (COL1A1), PFD plays a role in the attenuation of fibroblasts. PFD has also been exhibited to have either direct or indirect effects on interleukin-6 (IL-6), IL-12p40, IL-13, fibronectin, heat shock protein 47 (HSP47), and intercellular adhesion molecule one (ICAM1). It also suppresses the TGF-β-induced fibrotic processes in fibrotic fibroblasts by inversely regulating the collagen triple helix repeat-containing protein one (CTHRC1) [5]. PFD treatment reduced fibroblast proliferation and

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inhibited collagen production TNF-α, and the expression of iinterleukin1 beta (IL-1β); a cytokine that induces fibroblasts to produce fibrogenic mediators such as; PDGF [6,7]. Also, it plays an important role in reducing oxidative stress [8]. Oxidative stress markers have been identified in patients with fibrotic disorders of the liver, kidney, and lung. Reactive oxygen species (ROS) are implicated in epithelial cell damage, apoptosis, and induced myofibroblast proliferation [9], (Fig. 1).

1.1. History of PFD

In the 1970s, PFD was first mentioned in patients. It has anti-inflammatory and anti-fibrotic properties. In the 1990s, it was shown to have anti-fibrotic properties in a hamster model of bleomycin-induced lung fibrosis, paving the way for its development as a treatment for IPF [10,11]. PFD was approved by the European Commission in February 2011 for use in adults with mild-to-moderate IPF, and the drug was available in the European Union (EU) in September 2011 [12]. This followed the launch of the product in Japan in December 2008. PFD had sales of US $4.4 million in the year following its launch, according to IMS MIDAS 2011, and the compound annual growth rate in sales since its launch is an impressive 420 %, with total sales of $45 million. PFD had initially been developed as an anti-inflammatory agent, but then shifted to developing PFD as an anti-fibrotic agent, since it was found to have anti-fibrotic activity in a canine lung infection model as well as reducing fibrosis and improving lung function in a hamster model of bleomycin-induced lung injury [13,14]. In animal models of inflammation and lung fibrosis, PFD has anti-fibrotic and anti-inflammatory properties. At therapeutically relevant doses, PFD reduced the release of pro-inflammatory and pro-fibrotic cytokines in mice in response to an inflammatory stimulus [15,16].

1.2. Pharmacokinetics

1.2.1. Absorption

In comparison to the fasting state, PFD administration with food leads to a 50 % drop in C_{max} and a lower effect on AUC [17]. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50–66 years of age) in the fed state, the rate of PFD absorption slowed, while the AUC in the fed state was approximately 80–85 % of the AUC observed in the fasted state. A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that PFD be administered with food to reduce the incidence of nausea and dizziness [18].

1.2.2. Distribution

PFD binds to human plasma proteins, primarily to serum albumin [19]. The overall mean binding ranged from 50 % to 62 % in studies conducted *in vitro* (1 to 100 μg/mL) and *ex vivo*. The mean apparent oral steady-state volume of distribution is approximately 70 L, indicating that PFD distribution to tissues is modest [20].

1.2.3. Metabolism

PFD is metabolized primarily by CYP1A2, with minor contributions from other CYP isoenzymes such as CYP2C9, 2C19, 2D6, and 2E1. *In vitro* metabolism studies with hepatic microsomes show that PFD is metabolized primarily by CYP1A2, with minor contributions from other CYP isoenzymes such as CYP2C9 and 2C19. 5-Carboxy-PFD, the main metabolite, has no or just very modest pharmacological effect [21].

1.2.4. Excretion

PFD's oral clearance appears to be moderately saturable. The mean clearance was reduced by roughly 25 % over a dose of 801 mg three times a day in multiple doses. Dose-ranging trial in healthy older people given doses ranging from 267 mg to 1335 mg three times a day. The mean apparent terminal elimination half-life of PFD after a single dose was around 2.4 h in healthy older people.

2. Pharmacological effects of PFD

2.1. Anti-oxidant effects of PFD

PFD reduced lipid peroxidation while also restoring antioxidant enzymes (such as superoxide dismutase and catalase). PFD reduces bleomycin-induced lung fibrosis via decreasing oxidative stress pathways. Reduced ROS production and oxidative stress may be additional ways by which PFD's antifibrotic benefits are mediated, according to these preclinical investigations [22]. PFD has been found to inhibit the

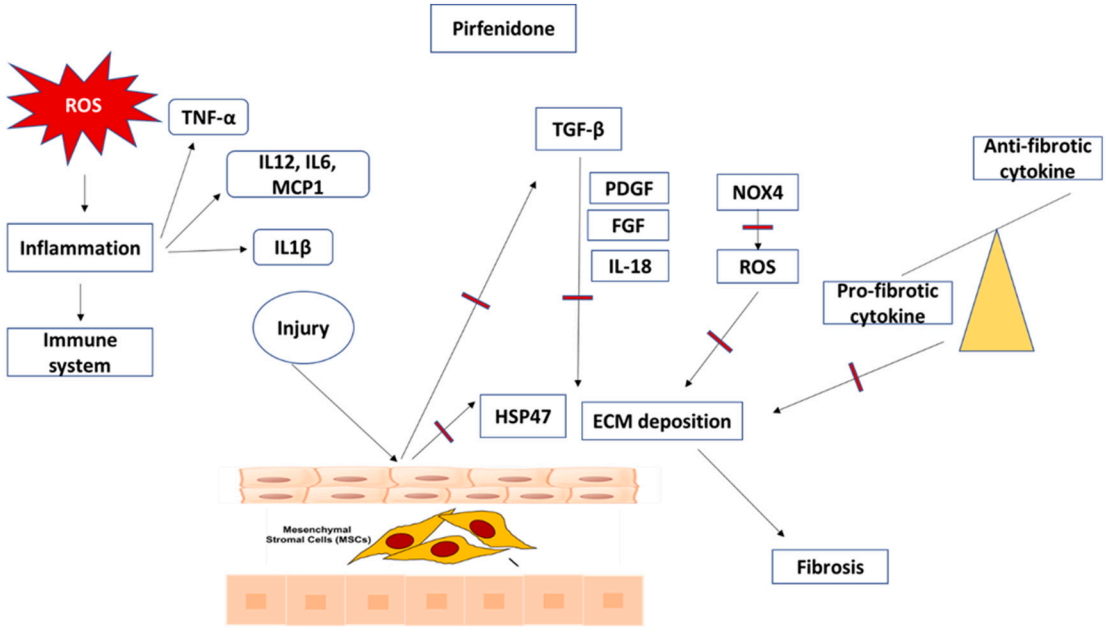

Fig. 1. Schematic diagram showing how the imbalance between profibrotic cytokines and the anti-fibrotic cytokines resulted in Excessive ECM deposition, activation of inflammatory pathway, and secretion of proinflammatory cytokines.

production of ROS by activated neutrophils and macrophages, as well as TGF-β, stimulated murine mesangial cells. PFD also reduced lipid peroxidation in microsomes in biochemical studies. The results of biochemical studies aimed at understanding the mechanism of antioxidant action have been conflicting. PFD has been shown to inhibit NADPH-dependent lipid peroxidation [23]. Inflammation, oxidative stress, and fibrogenesis are three important factors to consider when developing therapeutic strategies for liver cirrhosis [24]. Cirrhosis was treated with PFD or Diphenyleneiodonium (a potent known antioxidant). The study discovered a 60 % reduction in fibrosis index in the bile duct ligation model and a 42 % reduction in fibrosis index in the ccl4 model, as well as reduced inflammation [25]. Aside from the anti-fibrotic effect, the antioxidant and anti-inflammatory effects of PFD were discovered to be two of the drug's main pharmacological mechanisms [26]. One of the mechanisms of cytokine storm-inflammation-oxidative stress end-organ-damage and pulmonary toxicity is lipid peroxidation, which is initiated by generated superoxide in the cyclic reduction-oxidation. Cytoskeletal damage and lipid peroxidation are the other destructive effects of inflammation and severe oxidative stress due to cytokine storms. Hence, the antioxidant character of PFD makes it potent for the treatment of hyperimmune responses [27]. PFD is used safely in almost every clinic around the world, especially in the treatment of lung diseases [28]. It was used to treat oxidative damage in testicular tissue. The study found promising evidence for using PFD in routine urology practice to reduce the effects of testicular torsion on reproductive systems [29]. *In vitro* evidence suggests that PFD-approved agents for the treatment of IPF, exert anti-inflammatory and anti-oxidant effects. It exerts beneficial effects on specific markers of oxidative stress and inflammation in IPF patients [30,31], (Fig. 2).

2.2. Anti-inflammatory effects of PFD

PFD is an antifibrotic drug that also acts as an anti-inflammatory and antioxidant. PFD is used as a prophylactic measure to protect the kidney from I/R injury, as it prevents renal dysfunction and structural damage [32]. Dendritic cells (dcs) produce a range of proinflammatory cytokines, including colony-stimulating factor 3, IL-10, monocyte chemoattractant protein 1 (MCP-1), TNF receptor I, and TNF-α, which can be reduced by PFD [33]. To prevent pulmonary fibrosis, PFD reduces macrophage-driven cytokines such as; IL-1, TNF-α, TGF-β1, PDGF, and MCP-1, as well as macrophage numbers. *In vitro*, PFD was found to dramatically reduce TGF-β1 production in activated rat alveolar macrophages. PFD's capacity to reduce macrophage inflammatory activity is expected to be the main advantage of this drug, according to existing evidence [34]. PFD has been shown to exert significant anti-inflammatory and antioxidant effects in *in vitro* studies. In the study, 24-week treatment with PFD or nintedanib significantly increased glutathione (GSH) concentration. The anti-inflammatory activities of PFD have also been proven in cell-based studies. The most commonly reported effect of PFD in these studies is a reduction in TNF-α production. Other cytokines affected include IL-1, IL-6, and macrophage inflammatory protein-1. When activated by lipopolysaccharide (LPS), the anti-inflammatory cytokine IL-10 was likewise elevated by PFD injection. The anti-inflammatory activity of PFD has been demonstrated in a septic shock model in mice. Mitochondrial production of ROS activates the inflammasome and induces the synthesis and secretion of cytokines IL-1β and IL-18, which in turn leads to increased expression of pro-fibrotic factors such as TGF-β1 and PDGF. Inhibition of inflammasome formation might play a role in the anti-fibrotic and anti-inflammatory activities of PFD in pulmonary fibrosis, (Fig. 3).

2.2.1. Effects of PFD on brain injury

A traumatic brain injury (TBI) is a sudden biomechanical injury to the brain produced by a piercing force or when the head collides with an object. TBI outcome is heavily influenced by neuroinflammation. The secondary phase is linked to a deterioration in neurological outcomes. It is primarily made up of inflammation, which can have both positive and negative consequences [35]. The increased production of ROS as a result of microglia's rapid activation and migration to the trauma site, where they secrete proinflammatory cytokines and neurotoxic products, leads to oxidative stress, which leads to oxidative injury to lipids, DNA, proteins, and finally neurons [36]. PFD revealed anti-inflammatory and neuroprotective effectiveness along with a better neurological outcome. PFD proves to be valuable in decreasing brain injury and functional deficits after TBI by decreasing neuron-specific enolase (NSE), S-100B, and caspase-3 [37].

2.2.2. Effects of PFD on GIT injury

Inflammatory bowel disease (IBD), particularly Crohn's disease, frequently results in intestinal fibrosis, which leads to strictures that necessitate bowel resection [38]. Oral PFD administration reduced collagen deposition in colitis-associated fibrosis and inhibited the mRNA expression of col1a2, col3a1, and TGF-β [39]. Furthermore, both *in vitro* and *in vivo*, PFD reduced the activation of TGF-β-related smad and

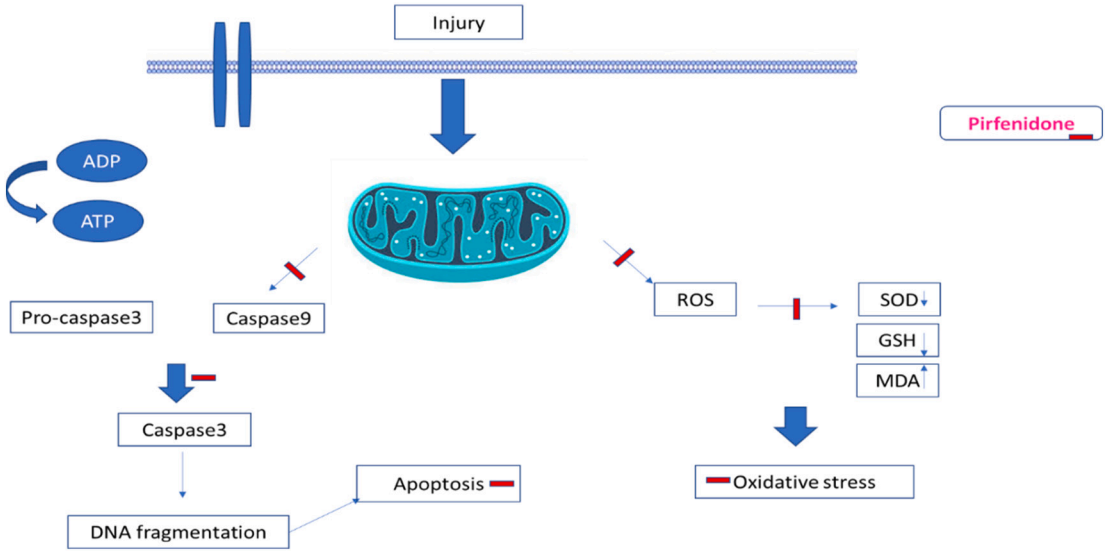

Fig. 2. Schematic diagram illustrates how injury participates in mitochondrial dysfunction, ROS release, activation of the apoptosis pathway, and DNA fragmentation.

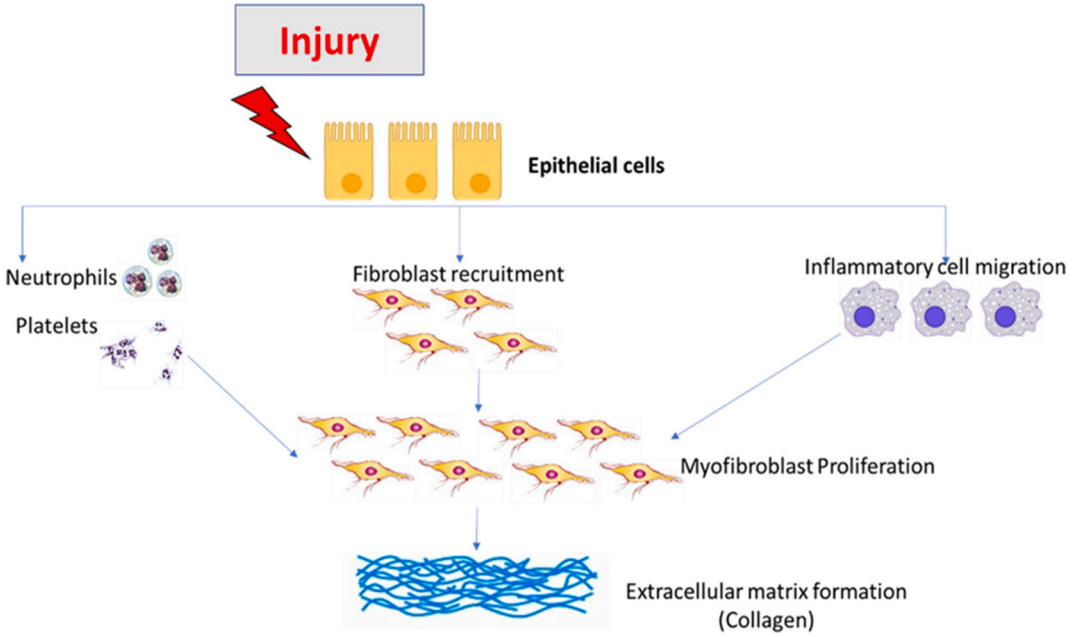

Fig. 3. Injury triggers the migration of inflammatory cells, the recruitment of fibroblasts, the growth of myofibroblasts, the production of extracellular matrix, and the deposition of collagen.

mitogen-activated protein kinase (MAPK) pathways. Jun N-terminal kinase 1 (JNK1), TGF-β1, IL1β, NF-κB, and caspase-3 were dramatically reduced by PFD therapy in a dose-dependent manner administered for the treatment of ulcerative colitis. PFD has retained the histological architecture of tissues considerably. PFD protects against AA-induced UC via regulating the TGF-β1/JNK1 and caspase-3 pathways, according to new research [40].

2.3. Anti-fibrotic effects of PFD

PFD is a pleiotropic chemical that facilitates tissue repair while inhibiting TGF-β, collagen synthesis, and fibroblast proliferation. This novel agent's anti-fibrotic effectiveness and safety have been demonstrated in lung, liver, and kidney tissue. PFD's anti-fibrotic action is achieved by a reduction in oxidative stress. PFD scavenges hydroxyl radicals and prevents NADPH-dependent microsomal lipid peroxidation [41]. PFD reduced oxidative stress caused by harmful hydroxyl radicals produced during differentiation of human lung fibroblasts and in bleomycin-induced pulmonary fibrosis in mice, possibly through inhibiting Nox4 (NADPH oxidase isoform 4) and Nox1. PFD was also discovered to limit the responder frequency of TCR-stimulated CD4+ cells *in vitro* and *in vivo*, as well as to drastically reduce Th2 cytokines in the bronchoalveolar lavage fluid of mice given a continuous allergen challenge to the airway using ovalbumin [42]. Furthermore, PFD suppresses the production of heat shock protein (HSP), a collagen-specific molecular chaperone involved in the intracellular processing of procollagen. PFD may also inhibit the epithelial-mesenchymal transition (EMT). Researchers investigated how the anti-fibrotic effect of PFD altered the function of T helper type 1 (Th1), Th2, and T regulatory (Treg) cells, all of which may play a role in peritoneal adhesions. PFD's preventive effect is stronger when given intraperitoneally, therefore systemic effects are low. As a result, PFD may be administered to prevent peritoneal adhesions after abdominal surgery [43]. A novel mechanism by which PFD inhibited JNK1 and MCP-1 pathways in mice, resulting in an anti-fibrotic effect. This adds to the evidence that PFD has anti-fibrotic capabilities, making it a promising option for countering doxorubicin cardiotoxicity by interfering with various cardiac fibrosis pathways. The findings pave the path for PFD to be used in combination with doxorubicin to treat a variety of tumors.

PFD, which regulates TGF-β1-induced fibrotic processes, is very sensitive to fibrotic fibroblasts. For predicting PFD response, a small number of patient fibroblast lines were employed. The reactions of fibroblasts obtained from patients with lung fibrosis to PFD were studied in functional tests in lung fibroblasts in order to anticipate PFD responses in lung fibrosis [44]. Furthermore, PFD inhibited the progression of angiotensin II (Ang II)-induced cardiac hypertrophy and fibrosis, implying that it could help prevent Ang II-induced cardiac hypertrophy. One of the PFD's key mechanisms may be TGF-β1 and, to a lesser extent, MR expression [45]. The efficacy data of PFD in reducing the progression of IPF in terms of decline in forced vital capacity (FVC) and in also reducing mortality rates compared with placebo [46]. Reversing existing fibrosis could enhance function and survival since fibrosis causes chronic degradation of heart and renal function. The synthesis and breakdown of extracellular matrix proteins are complicated, and there are numerous possible targets for pharmacological fibrosis reversal; nevertheless, TGF-β production or bioactivity suppression may be the most relevant. The findings suggest that using PFD to treat diabetic heart and kidney fibrosis and, more importantly, the functional impairment caused by increased collagen deposition is a viable mechanism for reversing fibrosis and functional impairment caused by increased collagen deposition. The activity of PFD was described in several well-characterized animal models of fibrosis in the lung, liver, heart, and kidney [47]. Treatment-related reductions in fibrosis are associated with modulation of cytokines and growth factors, with the most commonly reported effect being the reduction of TGF-β. The consistent antifibrotic activity of PFD in a broad array of animal models provides a strong preclinical rationale for the clinical characterization of PFD in pulmonary fibrosis and, potentially, other conditions [48].

Clinical investigation of PFD in IPF was initiated based on the broad antifibrotic activity observed in preclinical animal models. Several studies demonstrate a relationship between the reduction in fibrosis and improvements in related functional end-points, including improved lung function, improved heart function, reduced risk of cardiac arrhythmia, improved renal clearance, and reduction in biochemical markers of liver damage [49]. The effects of PFD on the expression of numerous growth factors and cytokines linked to fibrosis, including TGF-β, PDGF, and TNF-α, were studied. These findings are backed up by data from cell-based experiments that show the capacity to inhibit fibroblast

proliferation and regulate ECM deposition. Overall, PFD's preclinical profile shows systemic antifibrotic properties, supporting its clinical investigation in fibrotic disorders. PFD and 5-fluorouracil (5-FU) are effective in the treatment of keloid, a kind of fibroproliferative sickness with no recognized cause since they inhibit fibroblast development and decrease collagen deposition. When compared to PFD or 5-FU monotherapy, however, the combination of the two had a greater impact. PFD has been shown to inhibit the proliferation of human pulmonary artery smooth muscle cells (HPASMC) in IPF patients, indicating that it may be able to offset cell function abnormalities caused by prooxidant substances prevalent in IPF sera [50]. PFD exerted an effect on cellular proliferation, as indicated by reduced Ki67 protein level as well as G0/G1 arrest in the cell cycle in five different NSCLC cell lines [50]. Furthermore, core signaling pathway mediators demonstrated effects on their expression at the mRNA and protein levels, with PFD causing a differential gene expression response in three well-characterized gene sets containing SMAD3 downstream genes or TGF-β pathway members. In mesothelioma cell lines, hepatocellular carcinoma cells, and pancreatic cancer cells, a comparable effect on cell proliferation was recently discovered. PFD also impaired cellular mobility, as seen by decreased wound healing ability and migration, and resulted *in vivo* trials with a smaller vital tumor area [51]. By inhibiting the MAPK signaling pathway, PFD affects the balance of EMT *in vitro* and *in vivo*. The findings add to a growing body of evidence that PFD can help with renal fibrosis treatment [52]. In a unilateral ureteral obstruction (UUO) rat model, researchers looked at the effects of PFD on the EMT and renal fibrosis, as well as the molecular pathways implicated in cultured human renal proximal tubular epithelial cells (HK-2) [53].

2.3.1. PFD in idiopathic pulmonary fibrosis

Damage to the alveolar epithelium and disruption of alveolar basement membranes, the release of proinflammatory and profibrotic cytokines, myofibroblast activation and proliferation, and deposition of extracellular matrix proteins by mesenchymal cells all contribute to the development of IPF [54]. Biomechanical properties of the matrix environment that lead to increased lung stiffness may also stimulate fibroblast responses and fibrosis progression [55]. TGF-β and other profibrotic growth factors have been indicated as playing a significant role [16]. PFD has been demonstrated to protect hamsters against bleomycin-induced lung injury, and it inhibits TGF-β-induced myofibroblast development and fibrogenic activity in human lung fibroblasts [56]. Despite the lack of efficacy for many medicines that showed promise for the treatment of IPF, primary end goals were reached in Phase III, placebo-controlled, randomized clinical trials for both PFD and nintedanib. These findings led to FDA approval in 2014 for both medications to be prescribed for IPF patients in the United States [57]. PFD is presently being used to treat IPF patients in clinical studies, but it took several years for its benefits to be recognized, (Fig. 4 and Table 1).

PFD has a 2-year effect in slowing lung function decrease and lowering mortality in IPF patients when compared to non-antifibrotic medications [67]. Studies proved the effect of the first antifibrotic treatment in IPF on the results of randomized controlled trials in real-world settings. The findings of randomized controlled trials in real-world situations confirmed the effect of the first antifibrotic medication on IPF [68]. Patients on PFD had significantly longer than those on no antifibrotic medication, with more than half of those on PFD still alive compared to one-third of those on no antifibrotic treatment [69]. PFD is an anti-inflammatory and antifibrotic drug that works by regulating TGF-5 activity, TNF-α, and TNF-related pathways, as well as cellular oxidation [70]. In terms of pharmacology, PFD belongs to the immunosuppressive drug class. In 2011, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) authorized it as the first drug for the treatment of IPF [71]. According to supplementary studies, PFD medication benefited patients with advanced baseline lung function impairment recruited in the capacity and ascend trials without increasing the risk of dropout owing to adverse effects. [72]. Finally, real-world trials have indicated that PFD can aid to prevent FVC reductions in IPF, which is consistent with clinical trial results [73,74]. Reduced acute IPF exacerbation or collateral harm from disease severity are two possible causes of PFD minimizing respiratory-related hospitalization. Another study found that IPF patients admitted to the hospital for an acute exacerbation had a better prognosis. PFD was being used by these patients. The results of 11 patients in the PFD group and nine patients in the control group were compared [75].

2.3.2. PFD in cardiac fibrosis

Myocardial fibrosis is a natural response to a variety of cardiac stressors that can become maladaptive over time and contribute to the genesis and progression of heart failure [76]. Excess collagen buildup causes ECM expansion, which is thought to be a fundamental pathophysiological mechanism of HFpEF, a common pathway that exists regardless of aetiology. Myocardial fibrosis is an endogenous response to

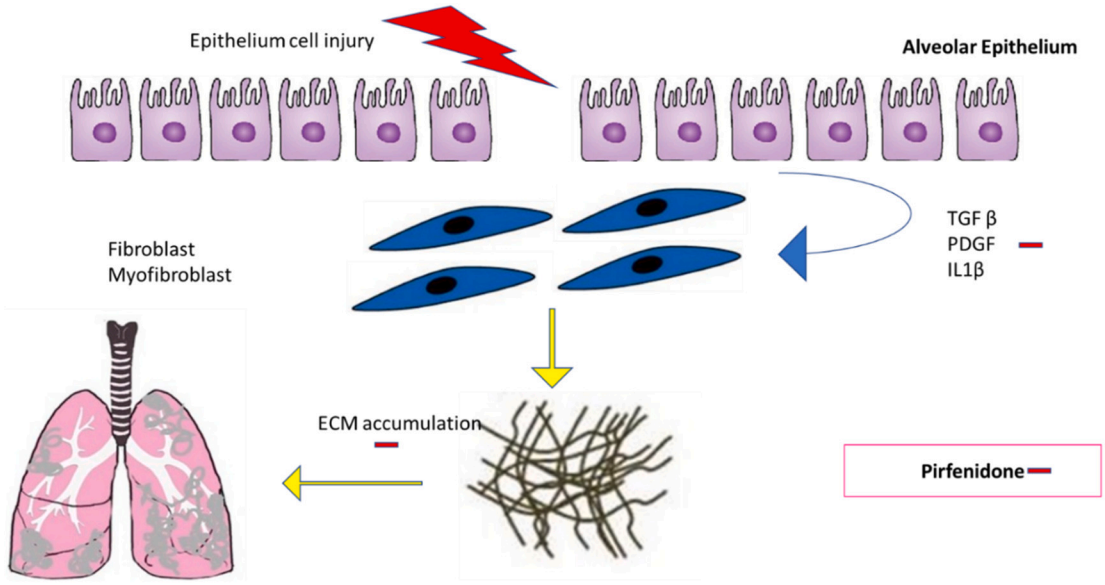

Fig. 4. Diagrammatic representation of the antifibrotic action of PFD against pulmonary fibrosis by inhibition of transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and interleukin 1 beta (IL1β).

Table 1
Clinical trials of PFD in the treatment of IPF.

Study type		Allocation	Intervention model description
1	Clinical trial	Randomized	In double-blind phase II clinical investigations in Japan, PFD was demonstrated to significantly reduce the pace of decline in forced vital capacity (FVC) in people with IPF [58,59]. Then, in phase III research, significant increases in advancement were discovered. These clinical trials paved the way for PFD to be approved for the treatment of IPF in Japan in 2008 [60]. Over 12 months indicated the benefits of PFD treatment in delaying the progression of IPF disease. PFD was observed to reduce all-cause mortality, FVC decline, and hospitalization risk, as well as boost exercise capacity, after 12 months [61].
2	Clinical trial	Randomized	For 52 weeks, 275 patients with IPF were randomly assigned to receive PFD 1800 mg/day (110 patients), PFD 1200 mg/day (56 patients), or placebo (109 patients) in a multicentre, randomized, double-blind trial. When compared to placebo, PFD 1800 or 1200 mg/day reduced the mean decline in vital capacity from baseline to week 52. When compared to placebo, PFD improved progression-free survival [62].
3	Clinical trial	Randomized	Non-steroid medicines were compared to placebo or steroids in adult patients with IPF. A total of 1155 participants were enrolled in four PFD placebo-controlled trials. PFD reduces the likelihood of disease progression by 30 %, according to the findings of a meta-analysis [63].
4	Clinical trial	Randomized	PFD's clinical efficacy in patients with IPF has been studied in three Phase III, randomized, double-blind, placebo-controlled studies. In Japan, the first Phase III clinical trial evaluating PFD's efficacy and safety in the treatment of patients with IPF was conducted. According to a Cochrane collaboration review [64], PFD appears to increase progression-free survival and, to a lesser extent, pulmonary function in individuals with IPF.
5	Clinical trial	Randomized	Many IPF disease progression events were included in the study, including a relative drop in % forced vital capacity (FVC) > 10 %, absolute decline in six-minute walk distance >50 m, respiratory-related hospitalization, and death. Patients on PFD had a lower risk of multiple disease progression episodes, and the difference was significant when compared to placebo [65].
6	Clinical trial	Randomized	A total of 170 patients from the same trials were enlisted in another study to determine how PFD affected advanced lung dysfunction. They had a more advanced kind of lung disease. PFD patients had a lower risk of all-cause mortality and less pulmonary function impairment than placebo patients [66].

many cardiac stressors that can become maladaptive over time and contribute to heart failure (HF) initiation and progression. Although fibrosis is a direct and indirect target of current HF medications, such as renin-angiotensin-aldosterone system inhibitors, its resistance to treatment necessitates the quest for novel, more specific approaches to myocardial fibrosis [77]. PFD is a tiny synthetic chemical that has a high oral bioavailability and has antifibrotic, anti-oxidant, and anti-inflammatory properties. PFD reduces cardiac fibroblast migratory ability, inhibits their proliferation and the process of myofibroblast differentiation (by inhibiting α-SMA expression), as well as myocardial fibroblast synthesis and secretion of TGF-β1, in a dose-dependent manner [78]. PFD also improves myocardial renin-angiotensin system imbalance and cardiac fibroblast synthesis and secretion of IL-10, an anti-fibrotic cytokine, via regulating ratios of myocardial MMPs and tissue inhibitors of metalloproteinases [79]. PFD appears to be a promising treatment for doxorubicin-induced cardiac fibrosis by blocking both JNK1 signaling and MCP-1 inflammatory pathways, preserving heart function [80]. PFD was shown to counteract and prevent myocardial remodeling and increased cardiac stiffness in hypertensive animal models. PFD reduced the course of Ang II-induced cardiac hypertrophy and fibrosis. PFD's ability to prevent cardiac fibrosis has also been demonstrated in streptozotocin-induced diabetic mice and rats were given intraperitoneal doxorubicin injections. PFD had a protective effect in dog models with HF caused by high-frequency left ventricular pacing, preventing atrial myocardial tissue fibrosis. The inhibition of several growth factors particularly TGF-β, but also PDGF and beta fibroblast growth factor (bFGF), matrix metalloproteinases, and pro-inflammatory mediators such as IL and TNF-α, as well as possible improvements in mitochondrial function and modulation of lymphocyte activation, have been attributed to these effects [41]. Because similar profibrotic pathways are activated in lung and heart disease, fibrosis plays a critical role in various cardiac ailments [81], and PFD has a broad spectrum of activity, it has been studied as a potential treatment for cardiac problems. PFD has been demonstrated to have cardioprotective benefits in animal experiments in a range of cardiomyopathy models [82]. PFD is presently being used to treat cardiac fibrosis patients in clinical studies, (Fig. 5 and Table 2).

2.3.3. PFD in renal fibrosis

Renal fibrosis, particularly tubulointerstitial fibrosis, is a prevalent end-stage of chronic kidney disease (CKD). Inflammatory cell infiltration, fibroblast activation, peritubular capillary loss, and tubular atrophy are all major cellular events in tubulointerstitial fibrosis. Mitochondria are energy-producing organelles that play an important role in the cell. In individuals with CKD, the mitochondrial respiratory machinery was found to be dysregulated [85]. The steady loss of renal energy caused by mitochondrial dysfunction may have a role in the structural aspects of CKD. Mitochondrial dysfunction plays a role in the pathogenesis of renal disease. Mitochondrial dysfunction in renal proximal tubular epithelial cells plays a role in EMT pathogenesis. The proximal tubular mitochondrial dysfunction was a significant pathogenic mechanism in MMA-related kidney disease. As a result, mitochondrial function restoration is advantageous in the treatment of CKD [86]. Tubulointerstitial fibrosis is characterized by an increase in renal tubular epithelial cell apoptosis [87]. Apoptosis of renal tubular epithelial cells is a crucial adverse event that contributes to chronic kidney damage and renal fibrosis. Mitochondria are at the heart of the intrinsic apoptosis pathway's signaling cascade, and mitochondrial malfunction enhances tubular cell death. Oxidative stress is caused by an imbalance in free radical production, which is exacerbated by mitochondrial failure, and oxidative stress in the kidney contributes to renal fibrosis. As a result, an efficient therapeutic to protect mitochondrial activity in renal tubular cells after injury could counteract apoptosis and oxidative stress, both of which have been linked to renal fibrosis inhibition [88].

Renal fibrosis is the final common pathway for nearly all types of kidney disease that advance to renal failure, and fibrosis progression is linked to kidney function loss [89]. The presence of persisting fibroblasts and myofibroblasts enhanced fibrogenic mediators (TGF-β, PDGF, and IL-1β), and an imbalance of metalloproteinases and inhibitors are all common cellular and molecular mediators of renal fibrosis [90] Several studies have shown that PFD can reduce renal fibrosis, including models involving partial nephrectomy, diabetic nephropathy, cyclosporine, and vanadate [91]. UUO is used to produce progressive tubulointerstitial fibrosis in one well-studied model of renal fibrosis [92]. Studies investigated the effects of PFD in two variations of the UUO model in rats. Over three weeks, fibrosis occurred due to constant blockage in one experiment. In this animal, prophylactic therapy with PFD (0.6–0.9 % in feed) reduced UUO-induced collagen deposition by 50 % and also reduced collagen and TGF-β mRNA expression [93], (Fig. 6).

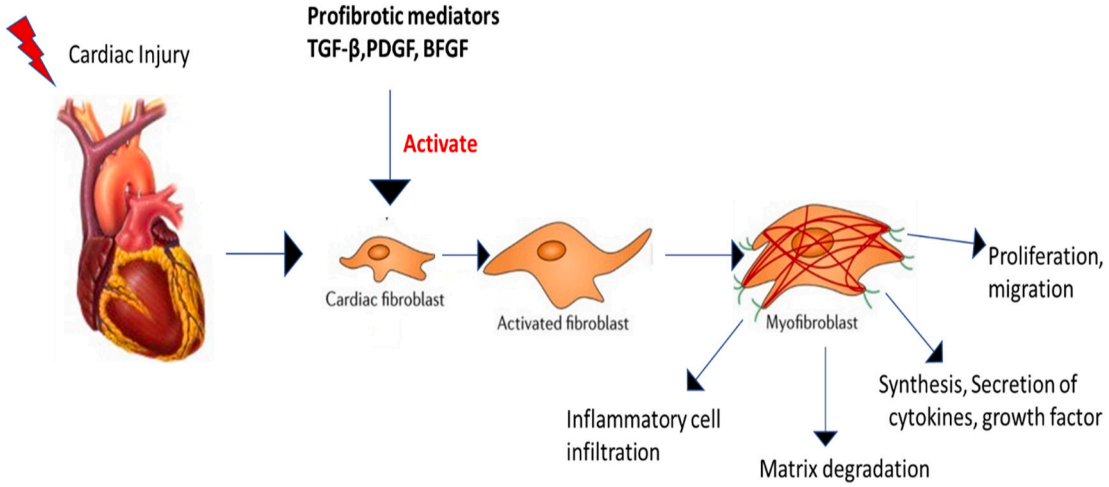

Fig. 5. Myofibroblast differentiation and functions of myofibroblasts after cardiac injury.

Table 2
Clinical trials of PFD in the treatment of cardiac fibrosis.

	Study type	Allocation	Intervention model description
1	Clinical trial	Randomized	A phase II trial examining the efficacy and safety of 52 weeks of PFD medication in patients with HFpEF with myocardial fibrosis (defined as extracellular matrix volume 27 % evaluated with cardiovascular magnetic resonance). The change in myocardial ECM volume is the study's primary endpoint. A sub-study will look into the link between myocardial fibrosis and myocardial energetics, as well as the effect of PFD on both. The experiment is still underway, and there is considerable interest in its findings, which could pave the way for better outcomes in HFpEF patients [83].
2	Clinical trial	Randomized	Patients with heart problems were enrolled in the double-blind, placebo-controlled trial. The efficacy and safety of PFD in patients with heart failure and preserved left ventricular ejection fraction phase II trial looked at the safety and efficacy of a 52-week treatment with PFD in 94 patients with HF and myocardial fibrosis (defined as an ECM volume of <27 % measured by cardiac magnetic resonance [CMR]). Extracellular volume decreased by 0.7 % in the PFD group and increased by 0.5 % in the placebo group at 52 weeks, with a very small between-group difference (also considering the variability in extracellular volume measurements by CMR), but statistical significance (−1.21 %; 95 % confidence interval, −2.12 to −0.31; $p = 0.009$). There was also a small but significant decrease in N-terminal pro-B-type natriuretic peptide levels [84].

2.3.4. PFD in hepatic fibrosis

Patients with persistent liver illness, such as viral hepatitis, alcoholism, or autoimmune liver disease, develop hepatic fibrosis [94]. Many of the same fibrogenic mediators found in other organs cause hepatic fibrosis, as do hepatic stellate cells, which, like myofibroblasts, are hyperactivated in terms of ECM deposition and growth factor synthesis [95]. Carbon tetrachloride (ccl4) poisoning causes increased liver enzymes and hepatic fibrosis in rats [96]. Studies assessed the efficacy of oral administration of PFD at (200 mg/kg). Treatment with PFD reduced liver fibrosis by 40 % and dramatically reduced collagen I mRNA expression. In PFD-treated animals, markers of liver damage (aspartate aminotransferase, alanine aminotransferase (ALT), total bilirubin, and direct bilirubin) were considerably lower than in controls, showing a functional advantage of PFD treatment [93].In the liver, PFD therapy lowered oxidative stress markers such as nitrites and malondialdehyde, which was followed by decreased expression of superoxide dismutase and catalase mRNAs [97]. Studied looked for the effects of PFD in two different versions of the ccl4-induced liver fibrosis model. Following the termination of ccl4, PFD medication led to a 70 % decrease in area stained positive for fibrosis and the number of hepatic stellate cells, as well as a 40 % reduction in total liver hydroxyproline [98].

Hepatic fibrosis reduction was linked to lower liver enzymes and fibrosis molecular markers. In a follow-up investigation, combining PFD with a continuous ccl4 insult reduced the region stained positive for fibrosis by 40 %. In the ccl4-induced liver fibrosis model, these findings show that PFD treatment can reduce fibrosis, change fibrosis molecular markers, and mitigate liver damage [99]. Another extensively used experimental paradigm in rats is dimethyl nitrosamine (DMN)-induced liver fibrosis, in which DMN causes liver remodeling and cirrhosis after prolonged administration [100]. Studies looked at PFD (0.5 % in feed; dosed in weeks 3–5 of a 5-week model) and discovered a 70 % reduction in the DMN-induced increase in the region of liver staining positive for fibrosis [101]. This was associated with significant reductions in ALT, necro-inflammatory score, hepatic stellate cell accumulation, and expression of TGF-β and procollagen-1 mRNAs. A second study demonstrated that PFD (500 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ via oral gavage) resulted in a 40 % decrease in the fibrotic area (via histopathology) with significant decreases in liver hydroxyproline content and expression of collagen I mrna [102]. Another extensively used model of liver fibrosis is bile duct ligation. PFD (200 mg/kg by oral gavage) was given to bile duct ligated rats and found a 60 % reduction in hepatic fibrosis (area stained with Masson's trichrome) and decreased expression of collagen I. In addition, PFD therapy reduced oxidative stress markers in the liver, such as nitrites and malondialdehyde, as well as the expression of superoxide dismutase and catalase mRNAs [103]. The PFD or other pharmacological treatments that inhibit protein glutathionylation can induce Glutaredoxin, which is a promising method for treating and preventing liver fibrosis [104], (Fig. 7).

2.4. Effects of PFD on mediators of fibrosis

PFD's ability to modulate the production of cytokines and growth factors, as well as to reduce oxidative stress, was investigated in several *in vivo* studies [105]. PFD also affects other fibrogenic mediators such as growth factors, chemokines, and matrix metalloproteinases (MMPs). Growth factor effects include the downregulation of PDGF and FGF. For fibroblasts, PDGF is a potent mitogen and chemoattractant. PDGF expression is increased in people with fibrotic diseases such as IPF,

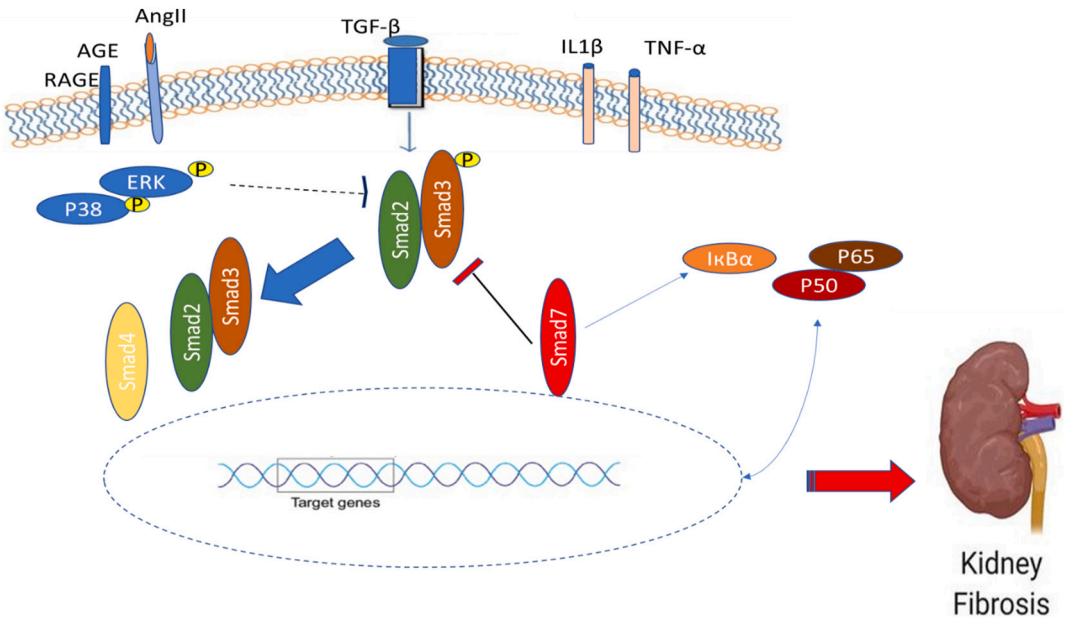

Fig. 6. Schematic diagram showing the effect of fibrogenic mediators on the induction of kidney fibrosis.

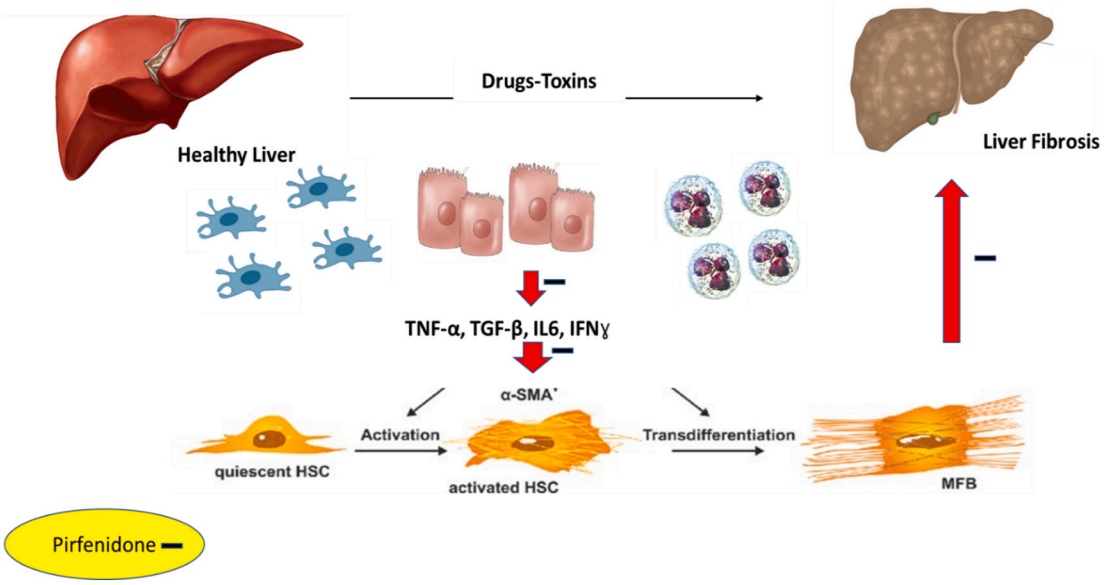

Fig. 7. Schematic diagrams showing how PFD protects against liver fibrosis through inhibiting TNF-α, TGF-β, IL6, IFNɣ, and α-SMA.

scleroderma, and bronchiolitis obliterans. In addition, PDGF promotes lung fibrosis in animal models induced by TGF-β, radiation, or bleomycin, and PDGF receptor tyrosine kinase activity inhibitors alleviate fibrosis. MMPs are substantially elevated in IPF and experimental lung fibrosis models. MMPs are known for degrading ECM proteins, but they may also be involved in fibrogenic growth factor activation or degradation, basement membrane disruption, and epithelial cell death. MMP-2 and MMP-9 production were both normalized by PFD in cardiac and renal fibrosis models, respectively. Both of these proteins have been connected to basement membrane disruption and be elevated in IPF patients [106]. A range of inflammatory cytokines that have been linked to the beginning and maintenance of fibrosis were altered by PFD therapy. TNF-α, for example, stimulates cell recruitment, fibroblast proliferation, epithelial cell hyperplasia, and death in airway epithelial cells. TNF-α overexpression causes inflammation and moderate fibrosis in rodent lungs. The treatment with PFD also reduced the expression of IL-1β, a cytokine that causes fibroblasts to create fibrogenic mediators like PDGF and TGF-β. In rodent lungs, IL-1β overexpression causes inflammation, tissue damage, and persistent fibrosis. PFD therapy inhibits the fibrogenic T-helper type 2 cytokines IL-4 and IL-13. Overexpression of IL-13 in mice results in increased expression of TGF-β and lung fibrosis, while IL-4 promotes ECM deposition [107]. PFD reduced oxidative stress markers in pulmonary and hepatic fibrosis models. Patients with fibrotic diseases of the liver, kidney, and lungs have been found to have higher oxidative stress markers. Reactive oxygen species, which are implicated in epithelial cell damage and apoptosis, are involved in TGF-induced myofibroblast proliferation, ECM production, and contractility. PFD's broad antifibrotic effects across a variety of fibrogenic mediator classes are consistent with its potent antifibrotic properties *in vivo* [47], (Fig. 8).

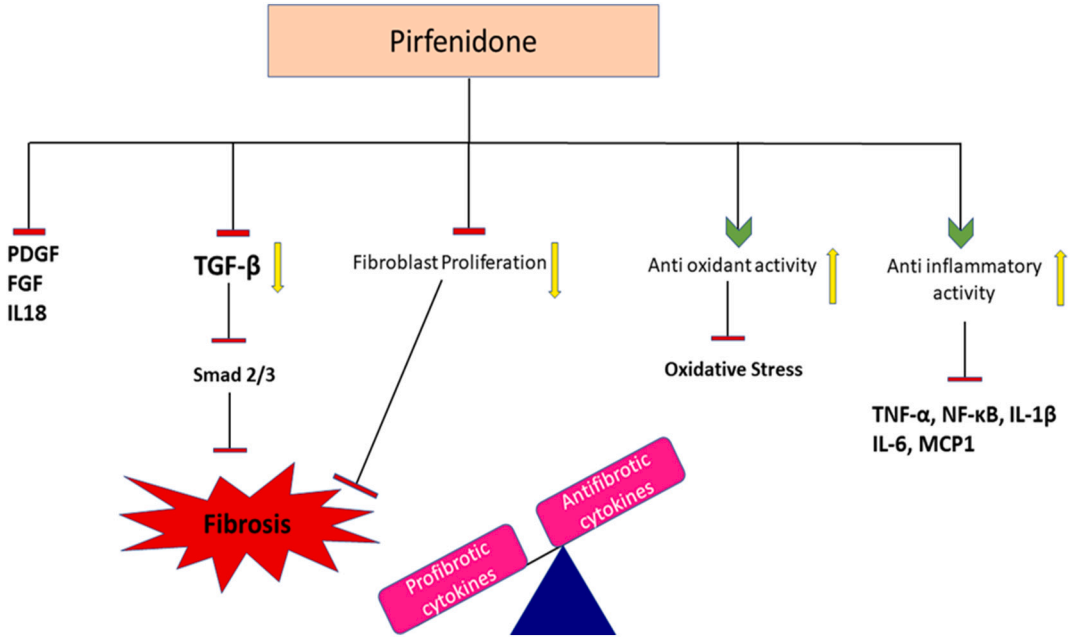

Fig. 8. Potential mechanisms for the suppression of fibrogenesis by PFD.

2.5. Effects of PFD in cell-based assays

In addition to affecting fibrotic mediators in animal models, PFD has been shown to exhibit a variety of activities in cell-based assays that could be linked to its anti-fibrotic properties. Reduced fibroblast and myofibroblast proliferation, suppression of extracellular matrix synthesis/deposition, and reductions in fibrotic markers are the three main antifibrotic effects of PFD *in vitro*. Each of these activities has been connected to the treatment of chronic fibrosis, is compatible with the effects of PFD in animal models, and may be necessary for the treatment of IPF with PFD [108].

PFD inhibits the NOX isoforms Nox4 and Nox1 and thereby reduces oxidative stress caused by harmful hydroxyl radicals (30). In a mouse model of paraquat-induced lung injury and fibrosis, PFD reduced lipid peroxidation while also restored antioxidant enzymes (such as superoxide dismutase and catalase) (28). In hamster trials, PFD reduces bleomycin-induced lung fibrosis via decreasing oxidative stress pathways (29, 45). Reduced ROS production and oxidative stress may be additional ways by which PFD's antifibrotic benefits are mediated, according to these preclinical investigations. PFD is used safely in almost every clinic worldwide, especially in lung pathologies. However, it was used against oxidative damage in testicular tissue for the first time in our study. We have obtained promising data for the use of PFD in routine urology practice in order to minimise the effects on reproductive systems of cases after testicular torsion. Our results must be supported by randomized prospective clinical trials.

2.6. Anti-apoptotic effects of PFD

PFD, on the other hand, has been shown to reduce apoptosis [109,110]. The potential protective role of PFD against L-arginine-induced acute pancreatitis (AP) in mice was assessed. The study provided evidence of the protective role of PFD against L-arginine-induced AP which counted on its anti-oxidative, anti-inflammatory, and anti-apoptotic effects. Hence, PFD might be a promising agent in the clinical treatment of AP [111–113]. In a chronic cyclosporine A (CSA) nephrotoxicity animal model, apoptosis was found to have a role in the advancement of fibrosis. In this model, the antifibrotic medication PFD was also demonstrated to suppress fibrosis. The effect of PFD on apoptosis-regulatory gene expression in the kidneys of CSA-treated rats was investigated. PFD's mechanism of action in the treatment of CSA-related fibrosis. It reduces apoptosis via altering the expression of apoptosis-regulatory genes [114]. In addition, PFD exerts an anti-apoptotic effect through inhibition of caspase 3 [40].

2.7. Anti-tumor effects of PFD

Targeting specific components of the tumor extracellular matrix to normalize the tumor microenvironment has recently been proposed as a means to decompress tumor blood vessels, promote vascular perfusion, and hence improve drug delivery and cancer therapy efficacy [115–118]. As a result, the researchers set out to discover safe and well-tolerated pharmacological compounds that could modify the microenvironment of solid tumors [119–123]. PFD's role in normalizing the tumor microenvironment was repurposed [124]. Cancer-associated fibroblasts (cafs) and the crosstalk between stromal and cancer cells may be useful in cancer management. Both primary cultured normal human lung fibroblasts and cafs were significantly inhibited in myofibroblast differentiation and activation by PFD. CAF activation was suppressed by PFD. PFD inhibited tumor-stroma crosstalk and suppressed tumor progression *in vivo*. PFD has the potential to inhibit not only fibroblast activity but also cancer cell-fibroblast crosstalk. From a variety of perspectives, PFD has a lot of promise as a novel treatment for non-small cell lung cancer NSCLC [125].

Idiopathic pulmonary fibrosis patients have a high risk of developing lung cancer [126], with few treatment options available. PFD monotherapy attenuated tumor growth with an increased T cell inflammatory signature in tumors. Co-administration of PFD with programmed death-ligand1 (PD-L1) blockades significantly delayed tumor growth and increased survival, compared with the effect of either treatment alone. Combination therapy promoted gene expression with a unique signature associated with innate and adaptive immune response resulting in the infiltration of immune cells and optimal T cell positioning. Furthermore, a great benefit of combination therapy is alleviating pulmonary fibrosis and reducing tumor growth in a tumor-fibrosis model. PFD facilitated antitumor immunity and enhanced the efficacy of PD-L1 blockades. It may act as an adjuvant to immunotherapy in cancer treatment, particularly, in lung cancer patients with pre-existing IPF. A novel function of PFD was identified, that it could enhance the antitumor effect of PD-L1 blockade by increasing the expression of cytokines and chemokines and

promoting T cell infiltration [127].

PFD successfully enhanced the recruitment of immune cells into the tumor [128]. Furthermore, by altering the immune cell composition in the TME toward induction of NK cells or T cells, PFD may act also on different layers: A direct anti-tumor effect targeting the proliferative potential of NSCLC cells and inducing pro-apoptotic molecules and an indirect anti-tumor effect by attracting NK and T cells [51]. Recent findings showed promising evidence of clinical efficacy in malignant diseases for inhibiting TGF alone or in combination with PD-L1, as it was discovered that a TGF gene expression signature in fibroblasts inhibited response to PD-L1 therapy in metastatic urothelial cancer, contributing to CD8 cell exclusion [129]. Restatement of TGF-β and PD-L1 leads to enhanced T cell penetration into malignancies, anti-tumor immunity, and cancer regression in a mouse model. Also, the bifunctional fusion protein M7824, which targets PDL1 and TGF 1, was used [130]. PFD has been shown to collaborate with cisplatin in killing cancer cells and cafs in NSCLC cells, as well as to enhance the effects of doxorubicin in inhibiting cancer fibrosis and TGF signaling in a triple-negative breast cancer (TNBC) model [131].

2.8. Effects of PFD against COVID-19

Coronavirus illness (COVID-19) is a global pandemic that has caused problems for public health and the economy [132–135]. In patients with COVID-19, cytokine storms, multiorgan failure, and especially acute respiratory distress syndrome (ARDS) are the major causes of mortality and morbidity [136–138]. The majority of COVID-19 sufferers die from a fulminant ARDS [139–141]. So far, >30 million individuals have been infected, with about a million dead [142]. Even though the world is still under the grip of the COVID-19 pandemic. On the other hand, COVID-19 patients developed lung fibrosis, a major danger to the prognosis of complications that required immediate treatment [143]. First, based on COVID-19 data, a possible mechanism for sarscov2-induced pulmonary fibrosis; (i) Direct evidence: pulmonary fibrosis was found in autopsy and pulmonary puncture pathology. (ii) Indirect evidence: increased levels of fibrosis-related cytokines in the peripheral blood of severe patients (TGF-β, TNF-α, interleukin (IL-6)) [144]. Several studies have investigated the clinical characteristics of the cytokine storm in COVID-19 patients. In extremely severe patients, elevated levels of IL-2 receptor (IL-2R), IL-6 as well as IL-10 were observed. Moreover, a gradual reduction in the absolute count of CD4+ T, CD8+ T, and B cells was also observed as the severity of the disease progressed. These findings suggested that there is a correlation between immune response and severity of COVID-19 progression. A study conducted on forty-three COVID-19 patients showed elevated IL-6 levels in severe cases and thus correlated to the severity of the disease. A retrospective multicentre study investigated the deceased and discharged COVID-19 cases. The study reported that elevated IL-6 was observed in deceased cases. Further, the cause of mortality in the deceased group was primarily due to respiratory failure (53 %). The evaluation of the clinical features in deceased COVID19 patients showed that a majority of deceased patients were associated with comorbidities, such as hypertension and cardiac anomalies. Further, the majority presented with complications, such as ARDS, respiratory failure, sepsis, acute cardiac injury, and heart failure. Moreover, the concentrations of IL-2R, IL-6, IL-8, IL-10, and TNF-α were also found to be elevated. A retrospective analysis of COVID-19 patients with pneumonia demonstrated an increased expression of serum IL-6. Furthermore, a decrease in the CD3, CD4, Natural Killer (NK), and CD8 cells were also observed.

Cytokine profiling of the peripheral blood samples obtained from severe patients revealed an increase in the levels of IL-6, IL10, IL-2, and IFN-γ [145–147]. Besides, it was also observed that the lymphocyte and T cell (especially CD8+ T) counts were substantially decreased while the neutrophil count was increased. Another study also showed increased levels of IL-2, IL-7, IL-10, and TNF-α. Further, it reported similar trends for granulocyte colony-stimulating factor (GCSF), C-X-C motif chemokine 10 (CXCL10), MCP-1, and macrophage inflammatory protein (MIP)-1 α Transcriptomic profiling of cytokines in SARS-CoV-2 infected patients have revealed elevated levels of cytokines MCP-1, CXCL10, MIP1α, and MIP-1β. Increased expression of CXCL10, IL-6, IL-8, MCP-1, RANTES (regulated on activation, normal T cell expressed and secreted), and TNF-α was also observed in severe COVID-19 patients [148–151]. The diabetic COVID-19 patients showed substantially increased leukocyte and neutrophil count. Further, elevated levels of IL-2R, IL-6, IL-8, and TNF-α were also observed. Altogether, the aforementioned findings indicated a pivotal role of cytokine storm in COVID-19 patients. Therefore, targeting the cytokine storm might help in attenuating the severity of disease progression, (Fig. 9).

PFD has been proven to have anti-inflammatory properties in several animal investigations and clinical trials. In numerous experiments, the antioxidant activity of PFD has been confirmed. Additionally, PFD's antifibrotic properties have been demonstrated in many clinical studies and are likely to lead to FDA approval of this medication for the treatment of IPF patients. Previously, studies used a combination of PFD, azithromycin, and prednisolone to successfully treat patients with post-H1N1 ARDS pulmonary fibrosis [152]. Additionally, PFD successfully enhanced the therapy of post-H1N1 ARDS fibrosis, so it seems fair to assess PFD's potential for treating COVID-19. Furthermore, PFD has been recommended and successfully used to treat ARDS brought on by exposure to white smoke. PFD, which inhibits fibroblast proliferation and extracellular matrix deposition in response to TGF-β1, PDGF, and other pro-inflammatory cytokines, was approved for use in China in 2013 for the treatment of IPF and unclassified interstitial lung disorders [153]. PFD is effective in many clinical trials against pro-fibrotic alterations brought on by SARS-CoV-2 and related inflammatory dysregulation as shown in the previous SARS epidemic. It has been demonstrated that early PFD administration in Covid-19 may reduce and even eliminate later immunological and inflammatory issues that result in pulmonary fibrotic alterations. As a result, the timing of PFD administration affects its efficacy in preventing pulmonary fibrosis; yet, PFD can treat persisting pulmonary fibrotic alterations in recovered Covid-19 patients with severe SARS-CoV-2 pneumonia. Since PFD is effective for post-inflammatory pulmonary fibrosis, it may have therapeutic effects against Covid-19 both in the early hyperinflammatory phase through inhibition of proinflammatory cytokines and in the late phase through an antifibrotic mechanism [154].

PFD may be the most effective drug in the treatment of pulmonary fibrosis [155]. Antiviral drugs and effective vaccines against SARS-CoV-2 are being developed; in the meantime, the best pharmacological goal is to manage all of the complications caused by this viral infection, primarily controlling the inflammatory and fibrotic state and preventing the infection from progressing to the most serious stages [156]. Many biological processes that lead to SARS-CoV-2 infection and acute respiratory distress syndrome share some similarities with IPF. Antifibrotic drugs like PFD may have therapeutic potential in preventing or reducing fibrotic lung lesions caused by ongoing COVID-19 infection, or in patients who have already recovered but still have fibrotic symptoms [157]. PFD is approved for the treatment of IPF in patients with mild to moderate disease. PFD could inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation by several mechanisms and ameliorate oxidative stress and hence protect pneumocytes and other cells from COVID-19 invasion and cytokine storm simultaneously. Based on the PFD mechanism of action and the known pathophysiology of COVID-19, PFD has the potential for the treatment of COVID-19 patients [158].

The COVID-19 scenario has heated the entire scientific community including those dealing with pulmonary fibrosis. The fibrotic sequelae of SARS-CoV-2 have given value to the anti-fibrotic therapies that are being evaluated to prevent the severity of the pandemic. It was in 2014 that two “umbrella” therapies were approved by the FDA for IPF management, nintedanib, and PFD, post which there are no significant additions in this field. Micro injuries to the alveolar epithelium are caused

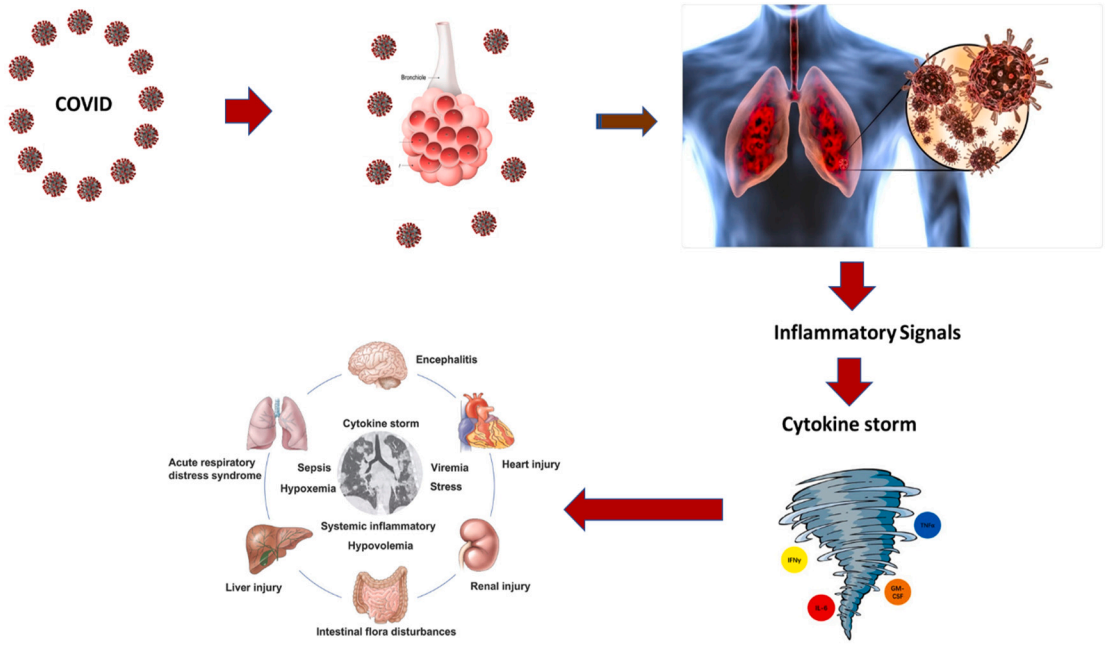

Fig. 9. Inflammatory response occurring during COVID-19 infection.

by a combination of genetic and environmental causes [159].

PFD could be used in the treatment of COVID-19-induced pulmonary fibrosis, with non-life-threatening side effects and possible beneficial effects. The persistence of lung parenchymal changes Post COVID-19 is increasingly recognized as a vital outcome observed in some patients recovering from SARS-CoV-2 infection with limited evidence-based management so far. The role of a combined therapeutic approach with anti-inflammatory and anti-fibrotic drugs might be provocative action in patients with COVID-19-related interstitial lung disease, especially those at risk for persistent long-term abnormalities and pulmonary fibrosis development [160]. COVID-19 pneumonia can lead to significant pulmonary fibrosis. Patients with pulmonary fibrosis after COVID- 19 pneumonia responded well to steroids and PFD [161]. PFD is presently being used to treat Covid19 patients in clinical studies (Table 3).

3. Summary of different actions of PFD showing the relation between them

Oxidative stress plays an important role in the activation of inflammatory pathways. The inflammation process, which is closely related to fibrosis, contributes to the release of a large range of inflammatory mediators that can contribute to either the induction of fibrosis (profibrotic) or the suppression of fibrosis (antifibrotic). Chronic inflammation, notably in the disease state, is characterized by a prolonged inflammatory response, destruction of tissues, and release of many inflammatory cytokines such as TNF-α. ROS damages biological molecules such as DNA, lipids, proteins, carbohydrates, and any other nearby molecule reversibly or irreversibly, resulting in a chain reaction that causes cellular damage Interestingly, free radicals from experimental models increased apoptotic activity. Moreover, Inflammation encourages all phases of carcinogenesis and predisposes to the growth of cancer. An inflammatory tumor microenvironment is created by the coordinated interactions of cancer cells with the stroma and inflammatory cells around them. One of the main characteristics of COVID-19 is the extreme inflammation that is sometimes seen in patients, especially in those who experience severe sickness. The aetiology of the illness is influenced by an overactive immune response that is mediated by a variety of cytokines. Numerous types of immune cells and inflammatory mediators have been linked to the development of various

Table 3
Clinical trials of PFD in treatment of Covid19.

	Study type	Allocation	Intervention model description
1	Clinical Trial	Randomized	Severe ARDS patients will be admitted to Soroka University Medical Center's specialized intensive care unit (ICU) after receiving an initial diagnosis of COVID-19 (day 0). Patients will be randomly assigned to one of the trial arms upon arrival and will either receive SoC alone or PFD 2403 mg delivered through the nasogastric tube as 801 mg TID (intervention arm) of the trial (control arm) [162].
2	Clinical Trial	Randomized	Comparing PFD with nintedanib for the treatment of fibrotic lung disease following COVID-19. The first dose of PFD will be 600 mg per day. Up until the desired amount of 2400 mg/day, the dose will be increased by 600 mg/day every 3–7 days. The maximally tolerated dose will be given to the subjects for a total of 24 weeks starting from randomization. Nintedanib will be given to the test subjects in this group twice a day at a dose of 150 mg. If there is an intolerance to the 300 mg/day dose, the dose will be decreased to 100 mg twice daily [144].
3	Clinical Trial	Randomized	The change in Forced Vital Capacity (FVC) (% predicted) at 6 months following treatment initiation with oral PFD versus placebo in patients with COVID-19-associated pulmonary fibrosis [163].
4	Clinical Trial	Randomized	Placebo; comparing the effect of PFD in avoiding establishing or progression of fibrosis induced after COVID-19 infection PFD; comparing the effect of PFD in avoiding establishing or progression of fibrosis induced after COVID19 infection [164].
5	Case report	–	66 years old female developed post-COVID-19 pulmonary fibrosis subsequently treated with PFD. Over 96 weeks after PFD treatment, her modified Medical Research Council Dyspnea level improved to 2 from 4 at discharge. Her 6 min walk test distance, total lung capacity, and diffusion capacity for carbon monoxide all increased [165].

diseases, according to studies. COVID-19 patients showed elevated levels of inflammatory mediators and increased levels of fibrosis-related cytokines in the peripheral blood of severe patients.

4. Conclusions

In conclusion, PFD has a significant role through its treatment in significantly reducing the incidence of multiple disease progression. The current review represented the mechanistic pathways by which PFD produces its effect. The observed improvement in its function was achieved through a variety of mechanisms, including (1) Antioxidant effect by reducing the oxidative stress, blocking the antioxidant inhibition, and enhancement of antioxidant defense cytokines; (2) Anti-inflammatory effect as evidenced by its capacity to suppress cytokine production, inflammatory cell accumulation, and inflammasome activation; (3) Anti-fibrotic effect via downregulation of the main profibrotic mediators as TGF-β, PDGF, JNK, MCP1, α-SMA, and other growth factors, it has therapeutic efficacy in the treatment of fibrotic diseases; (4) Anti-apoptotic effect through inhibition of caspase 3; (5) PFD's antitumor effect thereby inhibition of the production of PDGF-A, HGF, collagen type I, fibronectin, and periostin, factors that play important roles in tumor-stromal interactions in cancer. Therefore, combining PFD with traditional anticancer drugs may offer a promising treatment strategy for cancer; (6) PFD decreases inflammation by several mechanisms and ameliorates oxidative stress and hence protects pneumocytes and other cells from COVID-19 invasion and cytokine storm simultaneously. PFD's therapeutic application in IPF as well as its redistribution to treat fibrosis following COVID-19 and other related disorders were also clarified.

CRediT authorship contribution statement

Conceptualization, design, and construction of the conceptual framework of the review; Samar A. Antar and Ahmed A. Al-Karmalawy; **Literature search, collection, and draft preparation**; Samar A. Antar, Mohamed A. Saleh, and Ahmed A. Al-Karmalawy; **Data interpretation**; Samar A. Antar and Ahmed A. Al-Karmalawy; **Software**; Samar A. Antar; **Funding resources**; Mohamed A. Saleh and Ahmed A. Al-Karmalawy; **Original draft writing**; Samar A. Antar and Ahmed A. Al-Karmalawy; **Review and editing of the manuscript**; Samar A. Antar and Ahmed A. Al-Karmalawy. All authors have read and agreed to the submitted final version of the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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