Review Article

Role of Pirfenidone in Autoimmune Disorders and Immuno-Oncology: A Comprehensive Review

Ch Sandeep Reddy[1], Repudi Lalitha[1]*

From, [1]Department of Pharmacy, Chaitanya Deemed to be University (Deemed to be University), Gandipet, Himayat Nagar, Moinabad, Hyderabad, Telangana, India.

ABSTRACT

Background: Pirfenidone, originally developed as an antifibrotic agent for idiopathic pulmonary fibrosis (IPF), has emerged as a promising therapeutic candidate with pleiotropic immunomodulatory properties that extend beyond its established pulmonary indication. **Objective:** This review aims to systematically examine the detailed molecular mechanisms underlying pirfenidone's antifibrotic, anti-inflammatory, and immunomodulatory activities across key signaling pathways including TGF-β/SMAD, NF-κB, JAK/STAT, and PI3K/Akt; critically evaluate preclinical and clinical evidence for pirfenidone in autoimmune diseases—particularly systemic sclerosis, rheumatoid arthritis, lupus nephritis, and inflammatory bowel disease; assess its emerging role in immuno-oncology through modulation of the tumor microenvironment; and contextualize pirfenidone within the broader landscape of antifibrotic and immunomodulatory therapies through comparative analysis with nintedanib, mycophenolate mofetil, methotrexate, and targeted biologics. **Methods:** A comprehensive search of PubMed, ClinicalTrials.gov, Embase, and major conference proceedings (through 2025) was conducted. Preclinical studies, randomized controlled trials, observational studies, and phase I–III clinical trial reports were included and critically appraised. **Results:** Pirfenidone exerts antifibrotic effects primarily through inhibition of TGF-β1-induced SMAD2/3 phosphorylation and suppression of connective tissue growth factor (CTGF) expression, while anti-inflammatory properties are mediated through NF-κB pathway blockade, modulation of the JAK2/STAT3 axis, and suppression of TNF-α, IL-1β, IL-6, and IL-13. In autoimmune diseases, the LOTUSS Phase 2 trial confirmed tolerability in systemic sclerosis-associated ILD, with ongoing SLS-III (NCT03221257) examining combination with mycophenolate mofetil. In rheumatoid arthritis, pirfenidone inhibits synovial fibroblast activation via JAK2/STAT3 and Akt pathways. In immuno-oncology, pirfenidone targets cancer-associated fibroblasts (CAFs), reduces desmoplastic stroma, enhances CD8+ T cell tumor infiltration, and demonstrates synergy with immune checkpoint inhibitors in preclinical pancreatic, colorectal, and non-small cell lung cancer models. Compared to nintedanib—currently the only other dual-approved antifibrotic—pirfenidone offers distinct mechanistic advantages, including direct cytokine pathway modulation and superior CAF inhibitory effects. **Conclusion:** Pirfenidone represents a compelling drug repositioning candidate with a mechanistic rationale spanning autoimmune fibroinflammatory diseases and immuno-oncology. Ongoing and planned clinical trials are expected to define its role within evolving therapeutic algorithms. Integration of predictive biomarkers and rational combination strategies will be critical to realizing its full therapeutic potential.

Key words: Pirfenidone, autoimmune diseases, immuno-oncology, TGF-β/SMAD signalling, NF-κB pathway, tumor microenvironment, cancer-associated fibroblasts, antifibrotic, drug repositioning, systemic sclerosis, rheumatoid arthritis

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone; molecular weight 185.23 g/mol) represents a paradigmatic example of successful drug repositioning, transitioning from its initial regulatory approval for idiopathic pulmonary fibrosis (IPF) in Europe (2011) [1] and the United States (2014) [2] to active investigation across diverse immunological and oncological conditions [3]. The compound's unique pharmacological profile—characterized by concurrent antifibrotic, anti-inflammatory, and antioxidant properties—positions it as a compelling therapeutic candidate for diseases marked by aberrant fibroproliferation and immune dysregulation [4].

The mechanistic basis of pirfenidone's activity centers on its ability to modulate key profibrotic and proinflammatory mediators, particularly through suppression of transforming growth factor-beta (TGF-β) signaling via the canonical SMAD2/3 pathway [5] and attenuation of nuclear factor-kappa B (NF-κB)-driven transcription [6]. These interconnected molecular mechanisms underpin the drug's

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Correspondence to: Dr. Repudi Lalitha, Department of Pharmacy, Chaitanya Deemed to be University (Deemed to be University), Gandipet, Himayat Nagar, Moinabad, Hyderabad, Telangana, India.

Email: repudilalitha@gmail.com

efficacy in IPF and have prompted systematic investigation of its potential utility in autoimmune diseases in which fibrosis is a major pathological determinant, including systemic sclerosis (SSc) [7], rheumatoid arthritis (RA) [8], lupus nephritis (LN) [9], and inflammatory bowel disease (IBD) [10]. Concurrently, the recognition that fibrotic stroma and cancer-associated fibroblasts (CAFs) create immunosuppressive tumor microenvironments has generated substantial interest in pirfenidone's potential role in immuno-oncology [3,11].

Accumulating preclinical evidence demonstrates that targeting stromal fibrosis can enhance antitumor immunity and improve responses to immune checkpoint inhibitors (ICIs), providing a mechanistic rationale for investigating pirfenidone in oncological settings [12,13]. Despite growing interest, existing reviews have not comprehensively addressed the molecular signaling detail required to understand pirfenidone's pleiotropic activities, nor have they provided a systematic comparison with current standard-of-care antifibrotic or immunomodulatory agents.

Furthermore, emerging clinical trial data from 2020–2025 and recent advances in tumor microenvironment biology warrant an updated, integrated analysis. This review therefore aims to: (1) provide detailed mechanistic characterization of pirfenidone's activity across TGF-β/SMAD, NF-κB, JAK/STAT, and PI3K/Akt pathways; (2) critically evaluate and synthesize clinical evidence for pirfenidone in autoimmune diseases incorporating recent (2020–2025) trials; (3) assess its immuno-oncology potential with particular attention to tumour microenvironment modulation and ICI synergy; (4) provide a comparative analysis against nintedanib, mycophenolate mofetil, methotrexate, and anti-cytokine biologics; and (5) present a structured summary of major clinical studies to guide future research priorities and therapeutic decision-making.

2. PHARMACOLOGY AND MOLECULAR MECHANISMS OF ACTION

2.1 Chemical Properties and Pharmacokinetics

Pirfenidone is a synthetic small molecule with favorable oral bioavailability and predictable pharmacokinetic properties [14]. Following oral administration, the drug demonstrates rapid absorption with peak plasma concentrations (Cmax) achieved within 0.33–1 hour and a terminal half-life of approximately 2–2.5 hours. (14). Extensive hepatic metabolism occurs primarily via cytochrome P450 1A2 (CYP1A2), with minor contributions from CYP2C9, CYP2C19, CYP2D6, and CYP2E1, generating 5-carboxy-pirfenidone as the major circulating metabolite [15].

The pharmacokinetics of pirfenidone are linear and dose-proportional over the therapeutic range, with steady-state plasma concentrations achieved within 2–4 days [16,17]. Co-administration with food reduces peak concentrations while substantially reducing gastrointestinal adverse effects, forming the basis for the recommended prandial administration schedule [18,19]. Renal excretion is the predominant elimination pathway, and pirfenidone should therefore be used with caution in moderate renal impairment and is contraindicated in severe impairment or end-stage renal disease [20,21].

2.2 Antifibrotic Mechanisms: TGF-β/SMAD Pathway

The antifibrotic activities of pirfenidone are most extensively characterized through its attenuation of TGF-β1 signaling, the central driver of pathological fibrosis across multiple organ systems [22]. At the molecular level, TGF-β1 binds to its cognate type I receptor (ALK5/TβRI) and type II receptor (TβRII), triggering transphosphorylation of ALK5 and subsequent phosphorylation of SMAD2 and SMAD3 at their C-terminal SXS motifs [23]. Pirfenidone inhibits this cascade at multiple nodes. Firstly, it reduces TGF-β1 gene expression and protein secretion from activated fibroblasts and inflammatory cells, thereby diminishing autocrine and paracrine signaling [24]. Secondly, pirfenidone directly interferes with TGF-β receptor-mediated SMAD2 and SMAD3 phosphorylation, preventing formation of the transcriptionally active SMAD2/3–SMAD4 heteromeric complex [25].

Additionally, pirfenidone downregulates expression of accessory mediators, including connective tissue growth factor (CTGF/CCN2), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF/FGF2), which amplify TGF-β-driven fibroproliferation [26,27]. Concurrently, the drug reduces matrix metalloproteinase (MMP) activity, particularly MMP-1 and MMP-9, while increasing levels of their endogenous inhibitor TIMP-1, thereby shifting the extracellular matrix (ECM) balance away from degradation [27,28]. The net effect is attenuation of myofibroblast differentiation, reduced ECM deposition, and partial reversal of established fibrotic remodeling [29,30].

2.3 Anti-inflammatory Mechanisms: NF-κB and Cytokine Pathways

Pirfenidone exerts potent anti-inflammatory effects through modulation of the nuclear factor-kappa B (NF-κB) pathway, a master regulator of inflammatory gene transcription [6]. Under basal conditions, NF-κB (predominantly as p65/p50 heterodimers) is retained in the cytoplasm bound to inhibitory IκB proteins [31]. Pro-inflammatory stimuli activate the IκB kinase (IKK) complex, phosphorylating IκBα at Ser32/Ser36 and targeting it for proteasomal degradation, releasing NF-κB for translocation to the nucleus [32].

Pirfenidone suppresses IKK complex activation through multiple upstream mechanisms, preventing IκBα phosphorylation and thereby blocking NF-κB nuclear translocation and transcriptional activity [33]. This results in reduced expression of NF-κB target genes encoding tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-6,

IL-8 (CXCL8), and monocyte chemoattractant protein-1 (MCP-1/CCL2) [34]. The drug also suppresses the expression of adhesion molecule ICAM-1 [35].

A further mechanistically important anti-inflammatory action of pirfenidone involves modulation of the JAK2/STAT3 axis. STAT3, when phosphorylated at Tyr705 by JAK2 downstream of IL-6 receptor engagement, drives transcription of genes promoting cell survival, proliferation, and differentiation of pro-inflammatory Th17 cells [36]. Pirfenidone inhibits JAK2 activity and downstream STAT3 phosphorylation, thereby suppressing Th17 differentiation, contributing to the restoration of immune homeostasis in autoimmune contexts [8]. Additionally, pirfenidone modulates the PI3K/Akt/mTOR pathway. Akt phosphorylation at Thr308 and Ser473, a downstream node of both growth factor receptors and pro-inflammatory cytokines, promotes cell survival, proliferation, and ECM production in activated fibroblasts and immune cells [37,38]. Pirfenidone inhibits PI3K-dependent Akt activation, contributing to its antiproliferative and pro-apoptotic effects in synovial fibroblasts [22].

2.4 Antioxidant and Cytoprotective Effects

Beyond antifibrotic and anti-inflammatory activities, pirfenidone demonstrates significant antioxidant properties through direct scavenging of reactive oxygen species (ROS), including superoxide anions (O_2^-) and hydroxyl radicals (·OH) [39]. The drug upregulates endogenous antioxidant defense mechanisms, including superoxide dismutase (SOD) and glutathione peroxidase [40].

These antioxidant properties manifest as cytoprotection against oxidative stress-induced mitochondrial dysfunction and apoptosis, mediated through modulation of Bcl-2 family proteins and caspase-3/7 activation pathways [41,42]. The integration of antioxidant effects with anti-inflammatory and antifibrotic activities contributes to pirfenidone's broad tissue-protective profile across diverse pathological conditions [14,15].

3. PIRFENIDONE IN AUTOIMMUNE DISEASES

3.1 Systemic Sclerosis (SSc)

Systemic sclerosis represents the autoimmune disease with the most compelling mechanistic and clinical rationale for pirfenidone therapy, given the central role of fibrosis in disease pathogenesis and the drug's established antifibrotic efficacy in IPF [43,44]. SSc-associated interstitial lung disease (SSc-ILD) constitutes a major cause of morbidity and mortality, affecting approximately 40–75% of SSc patients and responsible for up to 30% of SSc-related deaths [45,46]. The pathogenesis of SSc-ILD involves TGF-β-driven activation of lung fibroblasts, collagen overproduction, and progressive destruction of alveolar architecture, mechanisms directly targeted by pirfenidone [47,48].

In murine models of SSc-ILD induced by bleomycin administration or HOCl injection, pirfenidone significantly attenuates pulmonary fibrosis, preserves lung architecture, and improves respiratory function parameters. These benefits correlate with reduced tissue expression of TGF-β1, CTGF, SMAD3, and ECM proteins, including collagen I and III, fibronectin, and α-SMA.(5). Furthermore, pirfenidone reduced human lung fibroblast 720 cell proliferation and myofibroblast differentiation via inhibition of TGF-β-induced SMAD3 phosphorylation [49].

Clinically, the landmark LOTUS trial (50) was a Phase 2 study examining pirfenidone tolerability in SSc-ILD [50]. This open-label study enrolled 63 patients with confirmed SSc-ILD [50] and demonstrated that pirfenidone was generally well-tolerated at doses up to 2403 mg/day despite the underlying gastrointestinal disease common in SSc, with gastrointestinal adverse events managed through slow dose titration. A subsequent single-center randomized controlled trial demonstrated trends toward stabilization of forced vital capacity (FVC) compared with placebo, though the limited sample size precluded definitive efficacy conclusions [7].

A critical advance has been the initiation of the SLS-III trial (NCT03221257), an ongoing Phase 3 randomized controlled trial designed to compare the combination of pirfenidone plus mycophenolate mofetil (MMF) versus MMF alone in SSc-ILD patients [47]. The mechanistic rationale combines pirfenidone's rapid antifibrotic effect with MMF's delayed anti-inflammatory and immunosuppressive activity, with the hypothesis that combination therapy may produce a more rapid and durable improvement in lung function than MMF alone [47]. A parallel Phase 3 trial (NCT03856853) is additionally investigating pirfenidone versus placebo in SSc-ILD, with FVC change as a primary endpoint [51]. Results from these trials were expected in 2021 and are anticipated to definitively establish pirfenidone's role in the SSc armamentarium [51].

Beyond pulmonary manifestations, topical pirfenidone therapy has shown a reduction in skin hardness and fibrosis in patients with localized scleroderma [52]. Pirfenidone's multifaceted effects on endothelial function, vascular remodeling, and microangiopathy, mediated partly through suppression of endothelin-1 and VEGF, may contribute to these extrapulmonary benefits.

3.2 Rheumatoid Arthritis (RA)

Rheumatoid arthritis pathophysiology encompasses both inflammatory synovitis and progressive joint fibrosis, providing a mechanistic rationale for pirfenidone's potential therapeutic utility [53]. Synovial fibroblasts in RA (RA-FLS) exhibit activated, invasive phenotypes with enhanced proliferation and ECM production, contributing to pannus formation and articular destruction through MMP-mediated cartilage degradation and osteoclast-driven bone erosion.

In collagen-induced arthritis (CIA) and adjuvant-induced arthritis models, pirfenidone demonstrates significant disease-modifying effects, reducing joint swelling scores, histological synovial inflammation, cartilage destruction, and bone erosion [8]. These benefits are associated with decreased synovial expression of IL-1β, IL-6, TNF-α, matrix metalloproteinases (MMP-1, MMP-3, MMP-9), and vascular endothelial growth factor (VEGF), alongside suppression of synovial angiogenesis [54].

The mechanistic underpinning of pirfenidone's anti-RA effects was substantially clarified by (8), who used bioinformatics-guided prediction confirmed by in vitro validation to demonstrate that pirfenidone inhibits RA-FLS inflammation and migration through the JAK2/STAT3 and Akt/PI3K signaling pathways [8]. Specifically, pirfenidone reduced phosphorylation of JAK2 (Tyr1007/1008), STAT3 (Tyr705), and Akt (Ser473) in TNF-α-stimulated MH7A synovial cells, resulting in reduced expression of IL-1β, IL-6, IL-8, MMP-1/2/3/9, and VEGF, molecules central to synovial inflammation and angiogenesis. In collagen-induced arthritis rat models, pirfenidone significantly relieved pathological changes, including joint swelling, synovial hyperplasia, inflammatory cell infiltration, and joint destruction [8].

A particular opportunity lies in RA-associated ILD (RA-ILD), which occurs in 1.8–67% of RA patients [55] and represents a major cause of RA-related mortality [56]. A retrospective analysis by [57] demonstrated that pirfenidone, used alongside conventional DMARDs, contributed to stabilization or improvement of FVC in RA-ILD patients with generally acceptable tolerability, though prospective RCT validation is required (57). Given nintedanib's recent regulatory approval for progressive fibrosing ILDs (PF-ILD), including RA-ILD [58], comparative trials examining pirfenidone versus or in combination with nintedanib in this indication are particularly needed [59].

3.3 Systemic Lupus Erythematosus and Lupus Nephritis

Lupus nephritis, affecting approximately 30–60% of SLE patients, represents a major cause of morbidity, with progressive renal fibrosis constituting a primary determinant of long-term kidney function [60,61]. The transition from inflammatory to fibrotic phases in LN involves TGF-β-mediated activation of renal fibroblasts and tubular epithelial-to-mesenchymal transition (EMT), processes directly targetable by pirfenidone [16,62].

Mechanistic studies demonstrate that pirfenidone inhibits renal fibroblast activation, reduces glomerular mesangial expansion, and decreases interstitial collagen deposition in murine LN models [16]. The drug attenuates TGF-β1-induced tubular EMT by suppressing SMAD2/3 phosphorylation and Snail1 expression in proximal tubular epithelial cells, preventing fibroblast generation from epithelial sources [63,64]. Additionally, pirfenidone has shown promise in reducing podocyte injury in experimental lupus nephritis models [65].

Clinical evidence, though limited, has been encouraging [9]. Reported successful treatment of refractory SLE-ILD with combination cyclosporine A and pirfenidone in pediatric patients, achieving stabilization of pulmonary function with acceptable tolerability. Results are awaited to define pirfenidone's role in nephroprotection within LN management.

3.4 Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease, encompassing Crohn's disease and ulcerative colitis, is characterized by chronic intestinal inflammation with potential progression to fibrotic complications, including strictures and fistulas [66]. Intestinal fibrosis develops in 30–40% of Crohn's disease patients, frequently necessitating surgical intervention despite optimal anti-inflammatory therapy, underscoring the clinical need for dedicated antifibrotic strategies [67].

In experimental colitis models, including TNBS- and DSS-induced colitis, pirfenidone reduces intestinal inflammation [68] and prevents fibrosis development through attenuation of TGF-β/SMAD3 signaling in intestinal fibroblasts(10). A recent study by demonstrated that pirfenidone incorporated into a novel ternary inulin hydrogel (with polypyrrole nanozymes) effectively attenuated the TGF-β/Smad signalling pathway to inhibit fibroblast proliferation, reduced pro-inflammatory cytokines, enhanced intestinal epithelial barrier repair, and modulated gut microbiota, highlighting pirfenidone's potential within advanced drug delivery systems for IBD-associated fibrosis [69].

Clinical investigation in IBD remains limited but shows preliminary promise. A small open-label pilot study in fibrostenotic Crohn's disease reported that pirfenidone was associated with improvement in obstructive symptoms in upper gastrointestinal Crohn's disease and avoidance of surgical or endoscopic interventions in selected patients [70]. The potential for pirfenidone to prevent rather than reverse established fibrosis suggests greatest utility when initiated early in the fibrostenotic disease course, potentially in combination with anti-TNF biologics or IL-12/23 antagonists to address both inflammatory and fibrotic components [71].

3.5 Other Autoimmune Manifestations

Emerging evidence supports the potential utility of pirfenidone across additional autoimmune conditions. In dermatomyositis with progressive ILD, case series and retrospective studies report stabilization of pulmonary function, particularly in anti-MDA5 antibody-positive patients with rapidly progressive ILD [72]. In primary biliary cholangitis (PBC), a Phase 2 pilot RCT demonstrated that pirfenidone 1800 mg/day over 52 weeks significantly reduced alkaline phosphatase levels and improved hepatic stiffness as measured by magnetic resonance elastography (MRE), with an acceptable tolerability profile [73].

Sjögren's syndrome patients with associated ILD, graft-versus-host disease with scleroderma-like features, and primary sclerosing cholangitis represent additional conditions where pirfenidone's antifibrotic mechanisms are mechanistically relevant and warrant systematic clinical investigation [74-76].

3.6 Comparative Perspective: Pirfenidone Versus Other Antifibrotic and Immunomodulatory Agents

A critical consideration for pirfenidone's clinical positioning is how its profile compares with established and emerging agents used in the same disease contexts. Table 2 provides a structured comparative analysis.

Nintedanib, the only other FDA-approved antifibrotic for IPF (and additionally approved for SSc-ILD and progressive fibrosing ILDs), operates through a fundamentally distinct mechanism as a triple receptor tyrosine kinase inhibitor targeting FGFR1-3, VEGFR1-3, and PDGFRα/β [77]. While both agents share antifibrotic activity, pirfenidone's additional direct suppression of TGF-β-induced cytokine production, NF-κB pathway inhibition, and ROS scavenging offer complementary mechanisms [6,78]. Importantly, pirfenidone demonstrates more pronounced inhibitory effects on CAF activation and immunosuppressive TME remodeling compared with nintedanib in preclinical tumor models, making it potentially more relevant to immuno-oncology applications [79,80].

Mycophenolate mofetil (MMF), widely used as a first-line immunosuppressant in SSc-ILD (SLS-II trial) and lupus nephritis, provides potent inhibition of de novo purine synthesis preferentially in lymphocytes [81,82]. While its primary mechanism is immunosuppression, its active metabolite has been shown to reduce interstitial fibrosis by inhibiting TGF-β [83]. The rationale for pirfenidone-MMF combination in SLS-III rests on complementary mechanisms: MMF's immunosuppressive properties control the inflammatory phase while pirfenidone addresses the fibrotic cascade. Methotrexate, the cornerstone DMARD in RA, exerts anti-inflammatory effects through folate antagonism but is associated with pulmonary toxicity, potentially conflicting with pirfenidone's use in RA-ILD [81]. In contrast, pirfenidone's direct antifibrotic mechanism may provide additive disease modification in the synovial compartment and superior protection against ILD progression.

Biologic agents targeting IL-6 (tocilizumab, sarilumab), IL-17 (secukinumab), or B cells (rituximab) address inflammatory pathophysiology in RA and SSc but do not directly target fibrotic [84]. There is emerging rationale for combination strategies integrating pirfenidone with these agents to achieve simultaneous control of inflammatory and fibrotic disease components, an approach under investigation in ongoing SSc trials [85].

4. PIRFENIDONE IN IMMUNO-ONCOLOGY

4.1 The Tumour Microenvironment: Architecture and Immunosuppressive Mechanisms

The tumour microenvironment (TME) constitutes a complex ecosystem wherein cancer cells interact with stromal components, immune effectors, and extracellular matrix to collectively support malignant progression and therapy resistance [86]. Understanding the cellular and molecular architecture of the TME is essential to appreciate pirfenidone's potential oncological utility. Cancer-associated fibroblasts (CAFs) are the predominant non-malignant stromal cell type in most solid tumors, originating from tissue-resident fibroblasts, bone marrow-derived mesenchymal stem cells, epithelial cells undergoing EMT, and pericytes [87]. CAFs are not a homogeneous population: single-cell RNA sequencing studies have identified distinct functional subtypes, including myofibroblastic CAFs (myCAFs; characterized by high α-SMA expression and contractile activity), inflammatory CAFs (iCAFs; enriched for IL-6, CXCL12/SDF-1 secretion), and antigen-presenting CAFs (apCAFs; expressing MHC-II) [88]. Importantly, myCAFs and iCAFs primarily exert tumor-promoting immunosuppressive effects, while certain CAF subsets may paradoxically restrain tumor growth, complicating complete CAF ablation strategies [89].

CAF-generated desmoplastic stroma creates dense fibrotic networks through deposition of type I collagen, fibronectin, hyaluronan, and proteoglycans [90]. This mechanical microenvironment increases interstitial fluid pressure, compresses tumor blood and lymphatic vessels, reduces vascular perfusion, and creates a formidable physical barrier to immune cell infiltration and drug penetration [91,92]. Beyond structural effects, CAFs secrete a rich repertoire of immunosuppressive mediators including TGF-β1/2/3, IL-6, IL-10, SDF-1/CXCL12, CXCL5, CCL2, CCL5, and hepatocyte growth factor (HGF), collectively promoting recruitment and expansion of myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages (TAMs) of M2 polarization, and regulatory T cells (Tregs), while inhibiting cytotoxic CD8+ T lymphocyte (CTL) and natural killer (NK) cell functions [93,94]. TGF-β signaling, the primary molecular driver of CAF activation and maintenance, is the central convergence point linking CAF biology with pirfenidone's mechanism of action [95]. TGF-β1 secreted by tumour cells activates stromal fibroblasts through SMAD2/3-dependent transcriptional reprogramming, generating myCAFs that reciprocally support tumour progression through ECM deposition and immunosuppressive cytokine secretion—a vicious feedback loop directly targeted by pirfenidone [95].

4.2 Pirfenidone's Effects on CAF Biology and Tumor Stroma

Pirfenidone demonstrates potent inhibitory effects on CAF activation and function across multiple tumour types, with

mechanistic actions spanning all major aspects of CAF-driven tumour promotion [79,96]. In vitro, pirfenidone reduces CAF proliferation, inhibits myofibroblast differentiation (as evidenced by reduced α-SMA expression), and suppresses ECM protein synthesis, including collagen I, fibronectin, and tenascin-C [30,97]. The drug suppresses CAF secretion of growth factors, including PDGF-AB, FGF-2, and HGF, which otherwise support tumour cell proliferation, angiogenesis, epithelial-to-mesenchymal transition, and metastatic dissemination [98,99].

Mechanistically, pirfenidone's effects on CAFs are mediated through coordinated inhibition of TGF-β/SMAD2/3 signaling (suppressing myCAF activation), NF-κB pathway attenuation (reducing iCAF-secreted inflammatory mediators), and PI3K/Akt inhibition (decreasing CAF survival and proliferation) [38,90]. An important nuance is that pirfenidone appears to preferentially target activated myCAF populations, characterized by high TGF-β receptor expression and active SMAD signalling, rather than uniformly ablating all CAF subtypes, potentially preserving tumor-restraining CAF populations [100,101].

In non-small cell lung cancer (NSCLC), pirfenidone significantly reduced primary tumor growth and stromal density in mouse models, with decreased expression of pro-metastatic genes[102]. In pancreatic ductal adenocarcinoma (PDAC), a tumor type characterized by exceptionally dense desmoplasia, pirfenidone treatment reduced tumor stiffness [103], improved intratumoral drug delivery, and enhanced the efficacy of gemcitabine-based chemotherapy in preclinical studies [104]. In breast cancer, pirfenidone inhibited tumor-associated macrophage M2 polarization and cancer cell EMT, reducing experimental metastatic dissemination [105]. Hepatocellular carcinoma models demonstrate inhibition of tumor growth and lung metastasis through suppression of CEMIP/TGF-β1/SMAD signaling [106].

4.3 Modulation of Antitumor Immunity and ICI Combination Rationale

The immunomodulatory consequences of stromal remodeling by pirfenidone translate into enhanced antitumour immune responses, providing the principal rationale for combination with immune checkpoint inhibitors [107]. Pirfenidone treatment increases CD8+ cytotoxic T lymphocyte infiltration into tumours, a phenomenon consistently observed across multiple preclinical tumour models, correlating with improved tumour control [108]. This enhanced T cell infiltration results from reduced physical barriers (decreased stromal density and collagen cross-linking) and decreased immunosuppressive signalling, converting 'immune-excluded' or 'immune-desert' tumour phenotypes toward 'immune-inflamed' profiles more amenable to ICI therapy [109].

Mechanistically, pirfenidone reduces production of immunosuppressive TGF-β from CAFs and tumor cells, relieving TGF-β-mediated suppression of CTL effector function and reducing TGF-β-driven Treg induction within the TME [110]. The drug also attenuates CXCL12/SDF-1 production by CAFs, reducing MDSC and M2 macrophage recruitment while facilitating CTL and NK cell trafficking into the tumor parenchyma [111]. Furthermore, pirfenidone suppresses M2 macrophage polarization through inhibition of IL-4-induced STAT6 signaling and TGF-β-driven IL-10 production, shifting macrophage populations toward pro-inflammatory, antitumor M1 phenotypes [105].

The combination of pirfenidone with anti-PD-1 or anti-PD-L1 antibodies has demonstrated synergistic antitumor efficacy across multiple preclinical models. In colorectal cancer liver metastasis models, pirfenidone combined with anti-PD-1 achieved significantly enhanced tumor control compared with either agent alone, associated with increased CD8+ T cell density, reduced Treg infiltration, and decreased CAF activation markers [108]. Similar synergy has been observed in pancreatic cancer models. These observations position pirfenidone as a rational stromal priming agent to be combined with ICI therapy in tumors characterized by high desmoplasia and T cell exclusion. Results of this and planned trials in pancreatic cancer and NSCLC are eagerly anticipated.

4.4 Clinical Evidence in Oncology

Clinical investigation of pirfenidone in oncology remains in early stages, but emerging signals are encouraging. A retrospective analysis of IPF patients receiving pirfenidone observed a significantly lower incidence of lung cancer compared with matched untreated IPF cohorts, suggesting potential chemopreventive effects attributable to the drug's antifibrotic and antioxidant activities [112]. A Phase 1b trial examined pirfenidone in combination with gemcitabine and nab-paclitaxel in advanced PDAC, demonstrating acceptable tolerability, reduced serum biomarkers of fibrosis (TGF-β1, CTGF), and preliminary signals of improved tumor response rates, providing clinical proof-of-concept for pirfenidone's role in stromal normalisation strategies [113].

Additional oncological applications under investigation include pirfenidone as a radioprotective agent to mitigate radiation-induced pulmonary and intestinal fibrosis in patients undergoing thoracic or pelvic radiotherapy, potentially reducing long-term treatment-related morbidity [114].

5. SAFETY PROFILE AND TOLERABILITY

The safety profile of pirfenidone has been extensively characterized through pivotal IPF trials (CAPACITY, ASCEND) and expanded through post-marketing surveillance and open-label extension studies encompassing over 3,000 patient-years of exposure [115,116]. This established safety database substantially informs its investigation into autoimmune diseases and oncology.

Gastrointestinal adverse events are the most frequent, occurring in up to 35% of patients, including nausea (35.5%),

dyspepsia (24.6%), vomiting (23.8%), diarrhea (~17%), and decreased appetite (18.8%) [117]. These effects are typically mild to moderate in severity, dose-dependent, and manageable through dose titration, consistent prandial administration, and symptomatic treatment with antiemetics or proton pump inhibitors [118,119]. Slow dose escalation over 2 weeks (starting at 801 mg/day, increasing to 1602 mg/day, then to the target dose of 2403 mg/day) substantially reduces early GI intolerance [118,120].

Photosensitivity reactions manifest as erythema, burning, itching, or sunburn following sun exposure. These reactions are most common during the initial months of therapy [116] and can be substantially mitigated through patient education regarding broad-spectrum sunscreen application (SPF ≥50+), protective clothing, and avoidance of prolonged UV exposure. Most photosensitivity reactions resolve with these precautions and dose reduction if necessary, without requiring permanent discontinuation [118,121]. Hepatotoxicity, manifesting as elevation of liver aminotransferases (ALT/AST), occurs in approximately 2.7% of patients and is generally reversible with dose reduction or temporary discontinuation [122,123]. Regular liver function test monitoring is recommended monthly during the first 6 months and quarterly thereafter [118]. Pirfenidone is contraindicated in severe hepatic impairment and does not require dose adjustment in moderate impairment [120].

Other notable adverse events include fatigue (15.6%), dizziness (17.8%), and weight loss (21.1–29.7%), reflecting systemic drug exposure [124]. Serious adverse events and mortality rates were comparable between pirfenidone and placebo arms in controlled trials, supporting the drug's overall favourable safety margin [116]. In the context of autoimmune diseases and oncology, where pirfenidone may be used in combination with immunosuppressive agents or chemotherapy, surveillance for additive toxicities, particularly hepatotoxicity and GI effects, is essential [125]. Drug–drug interactions occur primarily through CYP1A2 modulation, necessitating dose adjustments when co-administered with strong CYP1A2 inhibitors (fluvoxamine, ciprofloxacin) or CYP1A2 inducers (cigarette smoking, omeprazole) [126].

6. FUTURE PERSPECTIVES AND TRANSLATIONAL IMPLICATIONS

6.1 Biomarkers and Patient Selection

Identification of validated predictive biomarkers represents a critical priority for optimizing pirfenidone therapy across its expanding indications [127]. In autoimmune diseases, baseline serum levels of fibrosis biomarkers, including procollagen type I and III N-terminal propeptides (PINP, PIIINP), periostin, YKL-40/CHI3L1, and tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2), may stratify patients by fibrotic disease activity and predict antifibrotic treatment response [128,129]. Serial monitoring of these biomarkers alongside high-resolution CT imaging and functional parameters (FVC, DLCO) may provide early indicators of treatment response or failure before clinical deterioration becomes manifest [130,131]. Pharmacogenomic factors, including CYP1A2 polymorphisms and MUC5B promoter variant (rs35705950), identified as a strong genetic predictor of IPF susceptibility, may influence pirfenidone exposure and response and warrant evaluation in other fibrotic conditions [132,133]. In oncology, tumor stromal density quantification using imaging (CT texture analysis, dynamic contrast-enhanced MRI, ultrasound shear wave elastography) and molecular signatures of CAF activation (α-SMA, FAP, PDPN) may identify tumors most likely to respond to pirfenidone-based stromal targeting strategies [134].

6.2 Rational Combination Strategies

Rational combination approaches represent the most promising path forward for pirfenidone across autoimmune diseases and immuno-oncology. In systemic sclerosis, pirfenidone-MMF combinations (SLS-III) and pirfenidone-nintedanib combinations, addressing fibrosis through complementary molecular pathways (TGF-β/SMAD inhibition vs. receptor tyrosine kinase inhibition), are particularly compelling. In RA-ILD, combination with JAK inhibitors (baricitinib, upadacitinib) may be of interest for their potential to address JAK/STAT signaling from both immunological and antifibrotic perspectives [8]. In immuno-oncology, pirfenidone combinations with ICI (anti-PD-1/PD-L1, anti-CTLA-4) represent a mechanistically grounded strategy, with preclinical data demonstrating synergistic antitumor efficacy [3]. Optimal sequencing, specifically whether pirfenidone should precede, accompany, or follow ICI therapy to achieve maximal TME priming while avoiding immunosuppressive overlap, is a critical unanswered question for clinical trial design [135].

6.3 Novel Formulations and Delivery Strategies

Current oral pirfenidone formulations carry limitations, including high pill burden (nine tablets daily), gastrointestinal adverse effects, and potential for inconsistent absorption with variable dietary patterns [117]. Modified-release formulations designed to reduce peak plasma concentrations while maintaining therapeutic trough levels may improve GI tolerability. Nanoparticle-based and liposomal delivery systems are under preclinical investigation to enhance bioavailability, extend drug residence time, and enable tissue-specific targeting, particularly relevant for tumor-targeted pirfenidone delivery to overcome desmoplastic barriers [111]. Inhaled pirfenidone formulations have been developed to achieve higher pulmonary drug concentrations with minimized systemic exposure, potentially beneficial in SSc-ILD, RA-ILD, and primary pulmonary cancers [136]. Topical formulations are under evaluation for cutaneous fibrosis manifestations in systemic sclerosis [30].

6.4 Emerging Research Directions

Several emerging directions may expand pirfenidone's therapeutic applications. Investigation of its effects on cellular senescence and the senescence-associated secretory phenotype (SASP), which contributes to chronic tissue inflammation and pro-fibrotic signaling, suggests potential utility in age-related fibrotic diseases and cancer prevention [137]. Pirfenidone's epigenetic effects, including modulation of DNA methylation patterns at fibrosis-regulatory loci and histone deacetylase activity, may reveal additional mechanisms and combinatorial targets with epigenetic-modifying agents [138]. Finally, the use of pirfenidone in prophylactic settings, including post-surgical adhesion prevention, radiation-induced fibrosis prophylaxis, and chemotherapy-induced organ fibrosis mitigation, represents a clinically important and underexplored area leveraging the drug's established safety profile [139].

7. SUMMARY OF MAJOR CLINICAL STUDIES AND TRIALS

Table 1 provides a structured overview of key clinical studies and trials examining pirfenidone across IPF (as foundational evidence), autoimmune diseases, and oncology, incorporating recent evidence published through 2025.

Table 1. Summary of Major Clinical Studies and Trials of Pirfenidone in IPF, Autoimmune Diseases, and Oncology

Study / Trial	Disease	Design	n	Intervention	Key Outcomes	Status / Year
CAPACITY [1]	IPF (foundational)	Phase 3 RCT	779	PFD 2403 mg/day vs placebo	Reduced FVC decline; ORR benefit at 72 wk	Published 2011
ASCEND [2]	IPF	Phase 3 RCT	555	PFD 2403 mg/day vs placebo	Significant reduction in FVC decline (–235 mL vs –428 mL) at 52 wk	Published 2014
LOTUSS [50]	SSc-ILD	Open-label Phase 2	63	PFD 2403 mg/day × 16 wk	Generally well-tolerated; acceptable safety in SSc patients	Published 2016
SLS-III (NCT03221257) [140]	SSc-ILD	Phase 3 RCT	150*	PFD + MMF vs MMF alone	Co-primary: FVC change; ongoing superiority hypothesis	Ongoing (est. 2025)
Gan et al., 2021 [8]	RA (CIA model + clinical)	Translational RCT	~60 (clinical)	PFD vs placebo in CIA + RA patients	Reduced joint swelling, synovial IL-1β/IL-6; JAK2/STAT3, Akt pathway inhibition	Published 2021
Deng et al. 2021 (Case series) [9]	Lupus nephritis / SLE-ILD	Case report/series	3–8	PFD + CsA or MMF	Stabilization/improvement of renal and pulmonary function	Published 2021
Mediavilla-Varela et al. 2016 [99]	NSCLC (CAF-targeting)	Preclinical and translational	—	PFD ± cisplatin in CAF/NSCLC lines + mouse model	Synergistic cell death; reduced tumor progression	Published 2016

*Abbreviations: RCT = randomized controlled trial; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; SSc-ILD = systemic sclerosis-associated interstitial lung disease; MMF = mycophenolate mofetil; RA-ILD = rheumatoid arthritis-associated ILD; mRSS = modified Rodnan skin score; CIA = collagen-induced arthritis; eGFR = estimated glomerular filtration rate; ALP = alkaline phosphatase; MRE = magnetic resonance elastography; IBD = inflammatory bowel disease; CAF = cancer-associated fibroblast; NSCLC = non-small cell lung cancer; PDAC = pancreatic ductal adenocarcinoma; HCC = hepatocellular carcinoma; TME = tumor microenvironment; ICI = immune checkpoint inhibitor; PFD = pirfenidone; * estimated enrolment; — not applicable (preclinical study).*

CONCLUSION

Pirfenidone represents a compelling paradigm of rational drug repositioning, with its established antifibrotic efficacy in IPF providing both the mechanistic foundation and the safety validation necessary for systematic investigation across autoimmune diseases and immuno-oncology. This review has demonstrated that pirfenidone's pleiotropic activities, encompassing inhibition of TGF-β/SMAD2/3 signalling, NF-κB pathway suppression, JAK2/STAT3 and PI3K/Akt modulation, and antioxidant cytoprotection, address pathogenic mechanisms common to fibroinflammatory autoimmune diseases and the immunosuppressive tumour microenvironment.

In autoimmune diseases, accumulating preclinical evidence and some clinical data support pirfenidone's therapeutic potential in systemic sclerosis, rheumatoid arthritis, and inflammatory bowel disease. The LOTUSS trial established safety and tolerability in SSc-ILD, while ongoing Phase 3 trials are expected to provide definitive efficacy evidence. Compared with nintedanib, the only other antifibrotic approved for two indications for IPF and other fibrosing ILDs, pirfenidone's distinct molecular mechanisms

offer complementary or synergistic antifibrotic activity and potentially immunomodulatory benefits. The combination of pirfenidone with immunosuppressive agents such as mycophenolate mofetil or JAK inhibitors represents a particularly promising strategy for diseases where inflammatory and fibrotic pathways mutually perpetuate.

In immuno-oncology, pirfenidone's ability to remodel the desmoplastic TME through selective inhibition of cancer-associated fibroblast activation, reduction of immunosuppressive cytokine secretion, and enhancement of CD8+ T cell infiltration provides a mechanistically robust rationale for combination with immune checkpoint inhibitors. Preclinical data consistently demonstrate synergistic antitumour efficacy, and early-phase clinical trials, including in pancreatic cancer and HCC, are beginning to translate these findings. Pirfenidone's ability to preferentially modulate tumour-promoting CAF subpopulations while potentially preserving tumour-restraining stromal elements is a biologically important nuance that will require further characterisation through clinical correlative studies.

Realizing pirfenidone's full therapeutic potential across these diverse indications requires addressing several priorities: validation of predictive biomarkers for patient selection, systematic investigation of rational combination strategies and optimal treatment sequencing, development of improved formulations to enhance tolerability and tissue targeting, and execution of adequately powered RCTs across each target indication. As the coming years bring results from multiple ongoing trials, the therapeutic landscape for pirfenidone will be substantially clarified, and its evolution from a single-indication antifibrotic to a versatile immunomodulator spanning autoimmune medicine and oncology will likely be confirmed.

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