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Review

Potential Therapeutic Targets of Resveratrol in the Prevention and Treatment of Pulmonary Fibrosis

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Abstract

Pulmonary fibrosis (PF) is a feared component in over 200 interstitial pulmonary diseases, which are characterized by increased alveolar wall thickness, excessive scarring, and aberrant extracellular matrix restructuring that, ultimately, affect lung compliance and capacity. As a result of its broad range of biological activities, including antioxidant, anti-inflammatory, antiapoptotic, and many others, resveratrol has been shown to be an effective treatment for respiratory system diseases, including interstitial lung disease, infectious diseases, and lung cancer. This work reviews the known molecular therapeutic targets of resveratrol and its potential mechanisms of action in attenuating PF in respiratory diseases, including cancer, COVID-19, interstitial lung diseases (ILDs) of known etiologies, idiopathic interstitial pneumonia, and ILDs associated with systemic disorders, such as rheumatoid arthritis, systemic sclerosis, Schrödinger's syndrome, systemic lupus erythematosus, and pulmonary hypertension. The current issues and controversies related to the possible use of resveratrol as a pharmaceutical drug or supplement are also discussed.

Keywords: resveratrol; pulmonary fibrosis; interstitial lung diseases; SIRT1; TGF-β1; Nrf2

1. Introduction

Due to the associated perception of safety, natural compounds instead of synthetic ones are emerging as more desirable therapeutic tools [1–5]. In fact, over the past two decades, natural supplements have massively conquered the market, while scientific research associated with natural compounds has also extensively increased [6–11]. Nonetheless, despite the multitude of studies conducted on plant extracts and individual components, the final therapeutic constituent, whether a single molecule or the synergy of several constituents, remains to be clarified.

Among the current natural compounds being analyzed, resveratrol is a naturally occurring polyphenolic phytoalexin, which is present in multiple plants and aliments that possesses anti-inflammatory, antioxidant, vasculoprotective, neuroprotective, and anticancer activities [12–15]. Due to its extensive range of biological effects, resveratrol has become a widely studied molecule in the treatment of many pathologies, including respiratory system diseases [4,14,16–18].

Pulmonary fibrosis (PF) is the end stage of many diffuse respiratory diseases characterized by excessive extracellular matrix deposition, destruction of pulmonary parenchymal architecture, and loss of lung function, which in most cases leads to the patient's death [19]. Interstitial lung disease (ILD) refers to a diverse group of disorders that are characterized by varying degrees of inflammation and/or fibrosis in the lung parenchyma and interstitium [20], which includes idiopathic pulmonary fibrosis (IPF) [21]. PF can also be a shared component in connective tissue diseases (CTD), which are a heterogeneous group of inflammatory autoimmune disorders that affect different tissues and organs, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), polymyositis (PM)/dermatomyositis (DM), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD), which are commonly associated with ILDs [22]. Conversely, the development of PF can also occur secondary to viral pneumonia, especially during COVID-19 infection, and also in lung cancer [23]. Indeed, lung tumors in IPF patients develop preferentially in the periph-

eral adjacent zones rather than in the fibrotic areas, thereby showing different histologic distributions and immunohistochemical characteristics compared to non-IPF-associated lung tumors [24,25].

Furthermore, there is an ever-increasing body of evidence emphasizing the protective role of resveratrol in respiratory system diseases [18]. Additionally, the vast amount of current literature indicates that the therapeutic effects of resveratrol against PF-related pathologies are predominantly linked to its ability to induce sirtuin-1 (SIRT1) expression during oxidative stress, and inflammatory and apoptotic events, which ultimately suggests that it possesses a critical role in attenuating lung fibrosis development [26–30]. Our work provides an update on the current literature and focuses on both PF and the classical resveratrol-exerted effects, such as antioxidant, antifibrotic, and anticancer [18], alongside systematically and comprehensively reviewing and analyzing the common molecular mechanisms that inter-relate PF to both ILD and CTD as potential resveratrol targets. Here, we schematically describe the classical and specific therapeutic molecular targets of resveratrol that are potentially suggested to attenuate PF as a common component in both ILDs, as primary disorders, and in CTD related to ILD, as secondary disorders. Then, we highlight the molecular mechanisms in ILDs therapeutically targeted by resveratrol, and mechanisms believed to be dependently targeted in ILDs-related to CTD, to provide a new comprehensive panorama that will enhance the way for how resveratrol dosage and administration are visualized and understood in future clinical studies. In this context, we also provide an overview of the aspects regarding the current controversies on the use of resveratrol as a pharmaceutical drug or supplement.

2. Presentation of Resveratrol

Resveratrol is a natural stilbene monomer, which is chemically known as 3,5,4′-trihydroxystilbene, and exists as a yellow-tinged-white powder with the molecular formula of $C_{14}H_{12}O_3$. Resveratrol is structurally composed of two phenol rings: one with two OH groups at C-3 and C-5, and the other with one OH at C-4′; both rings are linked by a styrene double bond, which allows resveratrol to exist in both the cis and trans geometrical isomeric forms (Fig. 1).

The first report on resveratrol was published by Dr. Michio Takaoka, who studied a poisonous medicinal herb named *Veratrum grandiflorum* and led to the isolation and identification of this bioactive compound [31]. Plants produce resveratrol in response to external stimuli, such as mechanical harm, ultraviolet radiations, drastic environmental changes, microbial infection, and fungicides [32]. Resveratrol synthesis starts with a non-oxidative deamination reaction of two aromatic amino acids, named L-phenylalanine and L-tyrosine, which leads to the generation of cinnamic acid and 4-coumaric acid, respectively. The hydroxylation reaction catalyzed by cinnamate-4-hydroxylase converts the obtained cinnamic acid into 4-coumaric acid. Next, the transformation of 4-coumaric acid into 4-coumaroyl-CoA by the enzyme 4-coumaroyl CoA ligase generates an active intermediate, which is used by plants in normal growth conditions. Conversely, in stress conditions, the enzyme stilbene synthase (STS) works to condense a portion of the 4-coumaroyl-CoA to 3 molecules of malonyl-CoA through repeated decarboxylating reactions, to ultimately produce one molecule of resveratrol [33–37]. Resveratrol is abundantly present in many foods and food products, such as grapes, peanuts, plums, blueberries, olive oil, and hops [38,39] (Table 1).

3. Classical Mechanisms of Action for Resveratrol in Lung Injury and Pulmonary Fibrosis

3.1 Antioxidants Potential

Since oxidative stress and inflammation cause DNA damage and alveolar cell injuries, they play a crucial role in the pathogenesis and progression of lung diseases. Moreover, additional lifelong illnesses, such as cancer, metabolic diseases, and neurological and cardiovascular complications are also associated with oxidative stress [12]. It is also widely recognized, for example, that crosstalk between oxidative stress and inflammation in lung tissue can cause lung fibrosis and associated pulmonary diseases [21,77–83]. Resveratrol has been demonstrated to have free radical scavenging ability [84], antioxidant properties [85], and antioxidant enzyme expression modulatory activity [84], all of which can eventually attenuate oxidative stress-related diseases [86]. Indeed, resveratrol can exert its antioxidant ability by directly scavenging free radicals, including superoxide radical (O_2^-), hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and nitrogen dioxide (NO_2) [87–91]. This activity is due to its chemical structure, characterized by the presence of a conjugated double bond system [92] and hydroxyl groups in positions 3′, 4′, and 5′ on the ring [93,94]. Experiments exploring the scavenging activity of resveratrol on free radicals showed a strong efficiency with a dose of 30 µg/mL that was able to scavenge up to 19.5% and 71.8% of the H_2O_2 and O_2^- species, respectively [95].

Resveratrol has also been shown to indirectly scavenge free radicals through its modulatory effect on the expression and activity of antioxidant enzyme genes, such as superoxide dismutase (*SOD*), catalase (*CAT*), glutathione (*GSH*), and glutathione peroxidase (*GPX*) [96]. Moreover, other endogenous antioxidant enzymes appear to be involved in the resveratrol free radical scavenging mechanisms, including NADPH oxidase (O_2^-), xanthine oxidase (O_2^- and H_2O_2), mitochondrial respiratory chain enzyme (O_2^-), and endothelial nitric oxide synthase (eNOS) [93,97]. Resveratrol can also protect against oxidative stress-elicited damage by inhibiting lipid peroxidation, an effect attributed to its high lipophilicity and hydrophilicity [98–101].

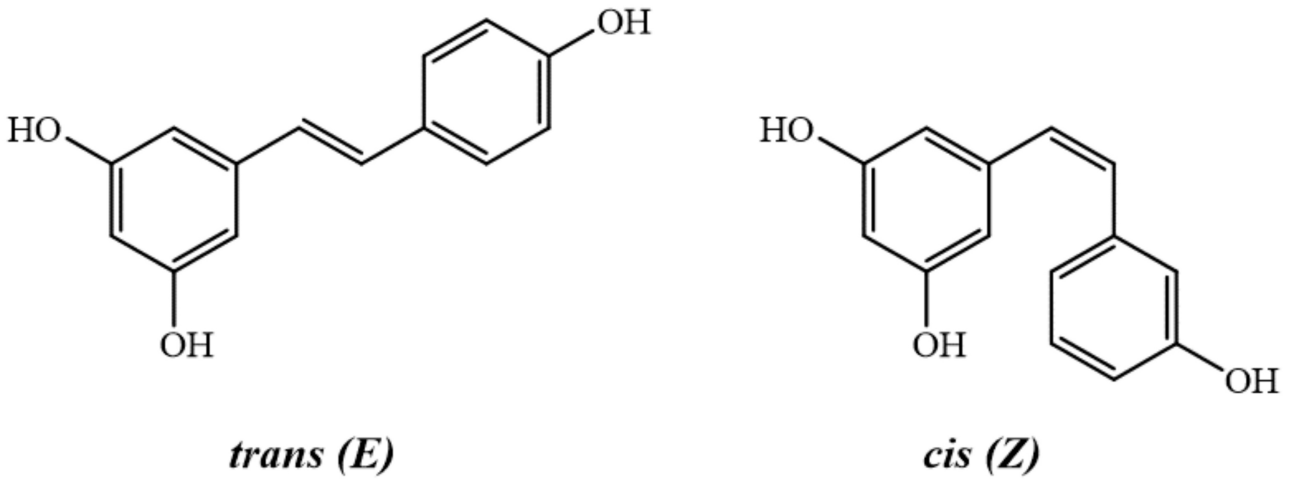

Fig. 1. Structures of *trans*- and *cis*- resveratrol.

Table 1. Resveratrol content in various food sources.

Source	Scientific name	Parts	Content (μg/g)	References
Grapes	*Vitis amurensis*	Leaves, stems, and roots	1.5–7.3	[40–42]
	V. betulifolia	Stems		[43,44]
	V. chunganensis	Whole plant		[45]
	V. coignetiae	Berries, stems, and leaves		[46,47]
	V. davidii	Stems		[48]
	V. labrusca	Berries, leaves, and stems		[49–53]
	V. pentagona	Stems		[48,54]
	V. riparia	Leaves		[54]
	V. riparia x, V. berlandieri	Roots		[54]
	V. rotundifolia	Berries		[50,54–58]
	V. thunbergii	Stems		[59]
	V. vinifera	Berries, cell suspension cultures, stems, and leaves		[35,60–63]
		Grape juice	0.12–0.26	[64]
Peanuts	*Arachis hypogaea* L.	Peanut kernels: raw and roasted	0.10–2.99	[65]
		Skins		[66]
		Roots		[67]
Blueberries	*Vaccinium corymbosum L.*	Fruit	86–170	[68,69]
Cranberries	*V. macrocarpon*	Fruit	90	[59]
Bilberries	*V. myrtillus* L.	Fruit	77	[70]
Pistachios	*Pistacia vera*	Kernel	6–69.7	[71]
Cocoa	*Theobroma cacao* L.	Powder	19–34	[64]
		Dark chocolate	3.8–6.5	[72]
		Milk chocolate	0.8–2.6	[64]
Plums	*Prunus domestica* (Arandana)	Skin and pulp	0.3–2.8	[73]
	P. domestica (Laetitia)	Skin and pulp	1.2–6.2	
	P. domestica (Red beauty)	Skin and pulp	0.3–0.9	
	P. salicina (Damask)	Skin and pulp	0.1–0.9	
	P. salicina (Golden Japan)	Skin and pulp	1.3–1.6	
	P. salicina (Metley)	Skin and pulp	0.2–0.4	
Dates	*Phoenix dactylifera* L.	Fruit	3.0	[74]
Tomato	*Solanum lycopersicum* L.	Fruit	0–2.1	
Itadori	*Reynoutria japonica*	Roots		[75]
		Tea		[76]

Interestingly, other signaling pathways were also found to be implicated in resveratrol-mediated oxidative stress attenuation. In a murine model, resveratrol attenuates LPS-induced epithelial–mesenchymal transition (EMT) and PF by suppressing oxidative stress and tumor growth factor β1 (TGF-β1) signaling [102]. Oxidative stress also forms the basis for other respiratory disorders, such as IPF, asthma, and chronic obstructive pulmonary disease (COPD) [21,103,104]. In this regard, by reducing necrosis factor-κB (NF-κB) activity and increasing heme oxygenase-1 (HO-1) expression, resveratrol can also induce protective effects against smoke-induced lung oxidative injury in mice [86]. Recent data obtained in lung epithelial cells indicated that resveratrol was able to reduce *Pseudomonas aeruginosa*- and Streptococcus pneumoniae-induced oxidative stress by upregulating glutathione peroxidase and decreasing reactive oxygen species (ROS) formation, intercellular adhesion molecules-1 (ICAM-1) levels, and human β-defensin-2 protein expression [85,105].

3.2 Anti-Inflammatory Potential

Inflammation is a localized protective response to tissue damage and/or microbial invasion, which serves to isolate and destroy the harmful agent and prepare the injured tissue for eventual repair and healing [106]. Chronic inflammation leads to tissue fibrosis [106]. The fibrosis of parenchymal organs (i.e., lung or other organs) is caused by prolonged injury, inflammatory diseases, deregulation of the normal wound healing processes, and extensive deposition of extracellular matrix (ECM) proteins [21,81,107]. In this context, it has been demonstrated that resveratrol activates several anti-inflammatory responses. In acute lung injuries, a fibrotic life-threatening condition, studies on animals demonstrated that resveratrol exerts a protective effect by inhibiting the myd88-dependent toll-like receptor 4 (TLR4) signaling pathway [108]. In lung tissue, such an effect is mediated by SIRT1 activation, decreased inflammatory cytokines, such as IL-1β, and macrophage inflammatory protein-1 alpha (MIP-1α), prevention of nitric oxide (NO) release, inhibition of the inducible NO-synthase (iNOS) expression, and suppression of NF-κB nuclear translocation [108]. In human airway epithelial cells, resveratrol exhibited anti-inflammatory activity more effectively, although it was less potent than glucocorticoids. Indeed, resveratrol was shown to inhibit *iNOS* and cyclooxygenase-2 (*COX-2*) gene transcription, along with IL-8 and granulocyte–macrophage colony-stimulating factor (GM-CSF) expression [109]. Fagone *et al*. (2011) [110] also demonstrated that resveratrol had an inhibitory effect on the TGF-β-induced deposition of α-smooth muscle actin (α–SMA) fibers, which is the hallmark of myofibroblast differentiation. The molecular mechanisms underlining such a phenomenon seem to be related to the TGF-β-mediated inhibition of both extracellular signal-regulated kinases 1/2 (ERK1/2) and Akt phosphorylation along with the restored expression of the tumor suppressor phosphatase and tensin homolog (PTEN) [110]. Interestingly, polydatin, a polyphenolic phytoalexin similar to resveratrol, has been reported to prevent bleomycin-induced PF by inhibiting the TGF-β/Smad/ERK pathway [111]. Using a mouse model, Zhao *et al*. (2016) [112] demonstrated that resveratrol protected the lungs from paraquat-induced acute injury by inhibiting NF-κB p65 translocation and cytokine production.

It is widely recognized that chronic inflammatory conditions are associated with cancer, especially in people of older ages [113]. A recent study performed in A549 lung cancer cells showed that the NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome was implicated in tumor-related inflammation and its progression [114]. Moreover, a significant marker of NLRP3 inflammasome activity is NF-κB pathway activation [115]. Likewise, increased TNF-α levels activate the NF-κB pathway, which upregulates IL-1β and IL-18 and causes NLRP3 activation [115]. Resveratrol has been shown to repress NLRP3 activation by suppressing the NF-κB pathway, thus, attenuating the multiplication of human A549 and H1299 cell lines and their metastatic potential [115].

Andrews *et al*. (2016) [116] showed that resveratrol was able to alleviate non-typeable *Haemophilus influenzae* (NTHi)-induced airway inflammation by upregulating a negative modulator of inflammation, the myeloid differentiation factor 88 (MyD88). Such an effect appears to be driven by a resveratrol-mediated, cAMP-PKA-dependent, inhibition of NTHi-induced ERK1/2 phosphorylation and an increase in mitogen-activated protein kinase phosphatase-1 (MKP-1) expression [116].

3.3 Anticancer Potential

Although the definitive molecular mechanisms are yet to be fully understood, compelling data indicated that resveratrol may be effective in inhibiting the occurrence and development of lung cancer [117]. Nonetheless, a wide range of data indicated that resveratrol anticancer properties were mediated through mechanisms such as apoptosis induction, autophagy regulation, cell cycle inhibition, angiogenesis suppression, and anti-oxidation [118]. In one study, resveratrol was reported to decrease cell viability, inhibit cell proliferation, and induce cell senescence and apoptosis by disrupting the intracellular antioxidant defense, increasing ROS production, and destroying lung cancer cell redox homeostasis [119]. Resveratrol has the ability to bind to the pro-oncogenic nuclear receptor 4A1 (NR4A1, Nur77), thereby hindering NR4A1-dependent transactivation in lung cancer cells. This implies that resveratrol can act as an NR4A1 antagonist and elicit effects similar to NR4A1 knockdown. Hence, resveratrol might be a promising therapeutic approach for lung cancer patients with high NR4A1 expression, which is considered a negative prognostic factor for certain types of solid tumor-derived cancers [120]. Interestingly, resver-

atrol can induce apoptosis and inhibit the viability of the small-cell lung cancer (SCLC) cell line H446. Indeed, this cancer currently lacks effective treatments, meaning that resveratrol can affect cell survival through a redox-dependent, PI3K/Akt/c-Myc-mediated signaling mechanism [121]. Moreover, resveratrol complexation with sulfobutylether-β-cyclodextrin (CD-RES) and its loading onto polymeric nanoparticles (NPs) enhance resveratrol anticancer activity against non-small cell lung carcinoma cells (NSCLC), thereby improving its therapeutic efficacy, compared to the sole resveratrol [122]. Such an effect is mediated by an enhanced cellular uptake, cytotoxicity, and apoptosis; thus, indicating CD-RES NPs as a potential resveratrol delivery system for NSCLC treatment [122]. A study investigating the mechanism related to cell death induced by resveratrol-loaded gelatin nanoparticles (RSV-GNPs) in NSCLC concluded that RSV-GNPs induced apoptosis, increased lipid peroxidative marker levels, and decreased antioxidant enzyme activities. RSV-GNPs also enhanced anticancer efficacy, which was associated with the altered expression of p53, p21, caspase-3, B cell leukemia/lymphoma 2 protein (BCL-2), BCL-2 associated protein X (Bax), and NF-κB, thereby indicating the involvement of a redox-mediated mechanism in NSCLC death [123]. Resveratrol was also reported to have antiproliferative and antioxidant properties in H460 lung cancer cells, with data indicating its ability to induce apoptosis through various mechanisms, including H_2O_2 production, Bid (a proapoptotic protein in the BCL-2 family), poly-ADP-ribose- polymerase -1 (PARP) and caspase-8 activation, and vascular endothelial growth factor (VEGF) downregulation [124]. The study also shows that inhibiting phosphorylated epithelial growth factor receptor (pEGFR) or pAkt enhances resveratrol's negative effect on cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (FLIP)-mediated cell viability and apoptosis, while supplementation with EGF or transfection with a wildtype-AKT (WT-AKT) plasmid inhibited apoptosis and the activation of proapoptotic proteins [124]. Mesenchymal stem cells (MSCs) can promote cancer cell growth and tumor formation due to their ability to secrete proinflammatory cytokines. In this context, a dose of 1 µM resveratrol can increase the reliability and safety of stem cell therapy by suppressing IL-6 and VEGF release from co-cultured A549 cancer cells and MSCs, thereby making it a potential candidate for combination therapy with stem cell treatment [125]. The *in vitro* effects of thymoquinone, caffeic acid phenyl ester (CAPE), and resveratrol were investigated in lung cancer cells and revealed an upregulation of apoptotic proteins, the downregulation of antiapoptotic proteins, and a reduction in the expression of cyclin D alongside an increase in p21 expression [126]. Resveratrol was also reported to inhibit migration and invasion of human metastatic lung and cervical cancer cells through the suppression of metalloproteinase (MMP)-9 expression and its transcriptional factors, NF-κB and AP-1, thereby suggesting its potential clinical use to prevent cell invasion by these cancers [127].

Resveratrol was indicated to decelerate the development of inflammatory chronic diseases [128]. Additionally, it was also suggested that the anti-inflammatory and anti-fibrotic action of resveratrol may promote a potential therapeutic effect toward pulmonary diseases with fibrotic complications [129] (Fig. 2).

4. Pulmonary Fibrosis, Interstitial Lung Diseases, and Associated Systemic Disorders

PF is a feared component in over 200 interstitial pulmonary diseases, which are characterized by reduced lung compliance and capacity as well as increased alveolar wall thickness [21,23]. Some of these diseases have known etiologies; however, many of them have a complex etiology that remains obscure or not fully elucidated [20]. ILD refers to a diverse group of disorders characterized by varying degrees of inflammation and/or fibrosis in the lung parenchyma and interstitium [22]. These diseases are broadly classified into different categories, including ILDs with a known etiology, which are those that occur from occupational/environmental factors, drugs, hypersensitivity reactions, and infections; ILDs associated with systemic disorders, such as sarcoidosis and collagen vascular disorders; rare miscellaneous conditions, such as eosinophilic granuloma, and the idiopathic interstitial pneumonias (IIPs) [20]. In the latter category, IPF figures as the most common form among the 27 known classes, while other forms include nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia (Fig. 3) [21].

IPF is a severe and progressive disease with limited treatment options, while exacerbations are associated with a high degree of morbidity and mortality [130]. Alternatively, the CTD-associated ILDs may share PF as an associated pattern. CTD is a heterogeneous group of inflammatory disorders that affect bone, cartilage, tendons, ligaments, muscle, joints, blood vessels, and specific organs [22]. Many CTDs, such as SLE, RA, SS, polymyositis (PM)/dermatomyositis (DM), SSc, and mixed connective tissue disease (MCTD), are autoimmune-mediated [22]. CTD-related interstitial lung disease (CTD-ILD) is one of the leading causes of CTD-associated morbidity and mortality. Clinically, CTD-ILD is highly heterogenous and involves rheumatic immunity and multiple manifestations of respiratory complications that affect the airways, vessels, lung parenchyma, pleura, and respiratory muscles [22]. The major CTD pathological feature is the chronic inflammation of blood vessels and connective tissues, which can progress and affect any organ, ultimately leading to multisystem damage [22]. The complex CTD-ILD etiology includes genetic risks, epigenetic changes, and dysregulated immu-

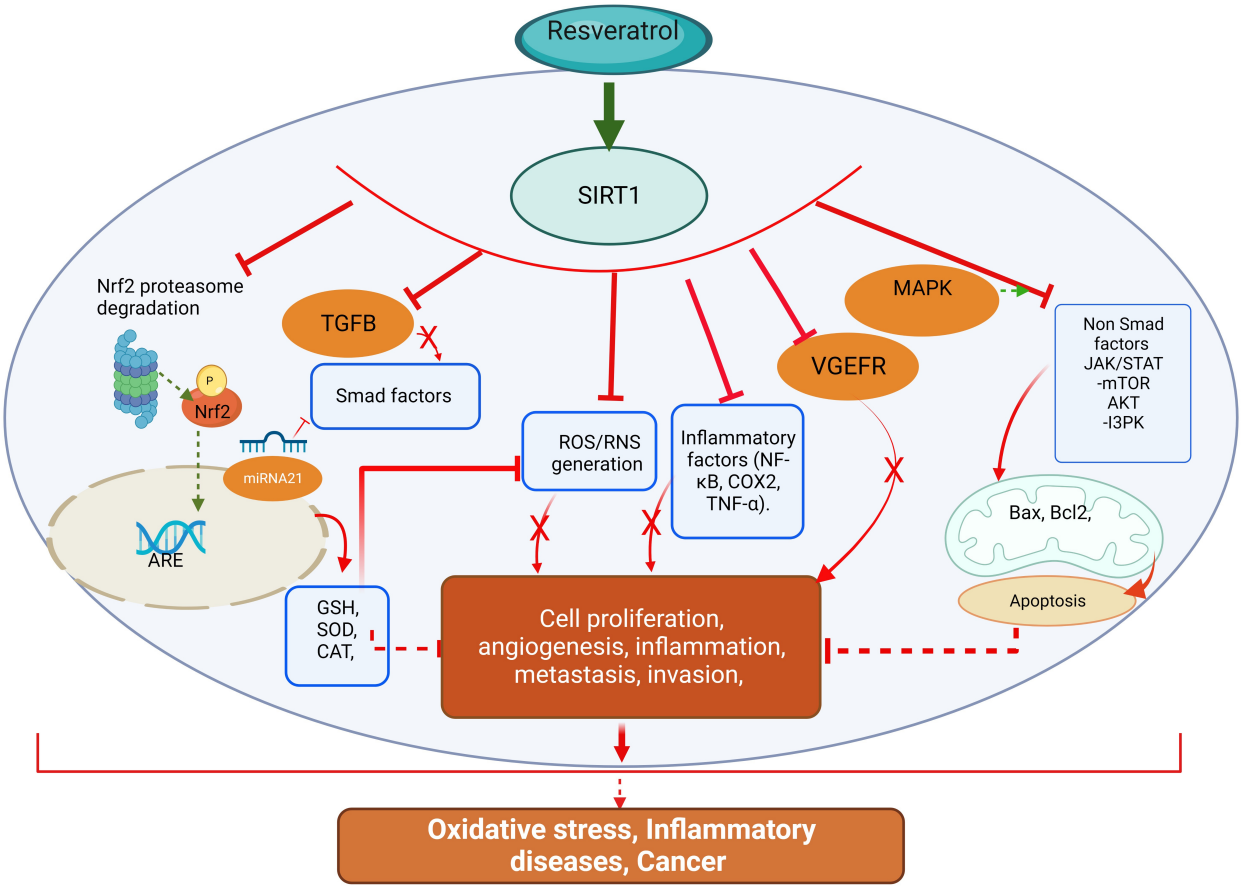

Fig. 2. Molecular pathways underpinning resveratrol antioxidant, anti-inflammatory, and anticancer effects. ARE, Antioxidant Response Elements; GSH, glutathione; SOD, dismutase; CAT, catalase; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-kappa B; COX2, Prostaglandin-endoperoxide synthase 2.

nity, which interact and lead to disease onset and development from various ill-defined environmental triggers [22]. CTD-ILD exhibits a broad spectrum of clinical manifestations, ranging from asymptomatic to severe dyspnea and from respiratory system single-organ involvement to multi-organ involvement [22]. The disease course is also featured by remissions and relapses, stability, or slow progression over several years to rapid deterioration, and presents highly progressive clinical manifestation from the onset of the disease. Currently, the diagnosis of CTD-ILD is primarily based on a distinct pathology subtype(s) and imaging, as well as the presence of related CTD and autoantibodies profiles. Meticulous comprehensive clinical and laboratory assessments to improve diagnostic processes and management strategies are much needed [22]. In this regard, heterogeneity and the lack of preclinical ILD and CTD-ILD pathogenesis models further complicate the establishment of an accurate diagnosis [131].

5. Pathogenesis, Etiology, and Treatment of PF in ILD and ILD-CTD

A great body of research on identifying the PF pathophysiological mechanisms is still ongoing owing to the diversified etiologies of this disease, which may result in different primary mechanisms that all lead to a common fibrotic outcome. PF patients share the common characteristic of a manifestation of excessive fibrotic components, which lead to the development of PF [132]. Moreover, they can extend to IPF following the development of a severe pulmonary fibrotic disease with an unknown insult [23].

The progression of PF may be stimulated by microenvironmental insults of intrinsic (genetic, age, and gender) or extrinsic origins (viral infections such as COVID-19, cigarette smoke, or occupational exposure to irradiations) targeting the alveolar epithelial cells (AECs), which are responsible for regulating many inflammatory aspects [23]. Following the initial insult, AECs initiate an immune response to counteract the microenvironmental insult, thereby promoting the resolution and repair of the damaged tissue. Nevertheless, if this process is not correctly performed, it will result in the formation of a perpetual fibrotic scar, which is characterized by ECM constituents, such as fibronectin, interstitial collagens, hyaluronic acid, and proteoglycans [133,134]. At the same time as the tissue injury occurs, endothelial cells and epithelial cells produce inflammatory mediators that activate antifibrinolytic-coagulation

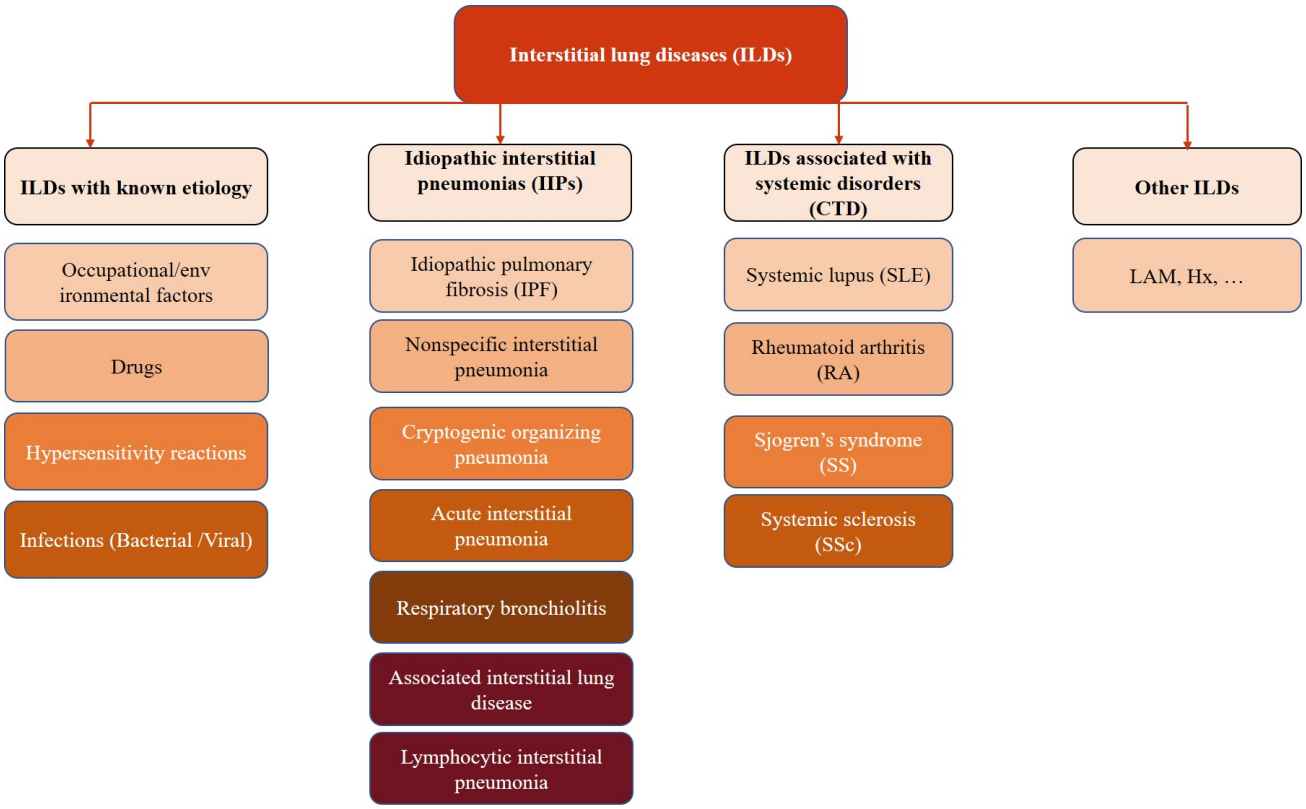

Fig. 3. Schematic summary of the different interstitial lung diseases.

mechanisms, resulting in ECM formation and deposition [135]. Platelet accumulation and the recruitment of inflammatory cells (e.g., eosinophils, macrophages, neutrophils, and lymphocytes) to the site of injury [136] induce a cascade of chemokines and cytokines that additionally enhances the inflammatory response and stimulates fibroblast proliferation and mobilization [137,138]. Generally, fibrosis occurs when the injury insult is aggressive or when the healing process mechanism is altered [135].

Conversely, the activation of myofibroblasts, which is responsible for collagen synthesis, alveolar epithelial type II cells (AEC2) apoptosis, and PF formation, is accompanied by a dysregulation in the immune response [139]. Inflammatory cytokines, including TGF-β, play a major and complex role in PF progression, primarily by modulating ECM deposition through myofibroblasts activation [140]. Additionally, TGF-β1 and other TGF-β species regulate cell recruitment to the sites of injury, induce fibroblast differentiation in the myofibroblast, stimulate ECM production by the myofibroblasts, and inhibit ECM degradation by the matrix metalloproteinases (MMPs) [134]. Under these conditions, the ERK- and Wnt/B-mediated augmentation in the secretion of the alveolar fibroblast growth factor (FGF)-2, in response to increased TGF-β1 activity, has also been reported [134]. Consonantly, ERK1/2 inhibition seems to attenuate fibrotic differentiation, while its overexpression appears to increase disease exacerbation and poor prognosis among IPF patients [141,142]. In addition to increased TGF-β signaling, fibrosis progression is also characterized by a shift of TH1 to TH2 [143], since the TH1 inflammatory profile, mainly characterized by the secretion of interferon-gamma (IFN)-γ and interleukin 12 (IL)-12, is responsible for fibrosis attenuation [144]. In contrast, the TH2 inflammatory profile, which is mainly defined by increased IL-4, IL-5, and IL-13 levels, is involved in inducing fibrosis [144]. Other cytokines, such as TNF-α, platelet-derived growth factor (PDGF), CXC chemokines, and IL-1a, have also been linked to IPF pathogenesis [145].

At a cellular level, previous studies have indicated the presence of extensive B cell infiltrations in lung tissue of SSc-ILD patients [146], while in RA-ILD, a prominent increase of follicular B cell hyperplasia and CD4+ cell number has been observed [147,148]. In RA-ILD and SSc-ILD patients, T cells release fibrogenic mediators, which subsequently stimulate fibroblasts and prime the fibrotic response [149]. Toll-like receptors (TLRs), which are critical components of innate immunity, have multifaceted effects on ILD in patients with CTD; indeed, they have been proposed as markers of ILD progression [150]. Correlation studies showed that TLR2 [151] and TLR9 [152] are profibrotic, while TLR3 [153] is antifibrotic in PF. On the other hand, TLR4 can be either profibrotic [154] or antifibrotic [155] depending on the micro-environment. However, the contribution of other innate players on CTD-ILD remains to be explored [22].

Promoting myofibroblast development is another mechanism through which the lungs respond to insults or injuries. Myofibroblasts are responsible for ECM secretion within the damaged area, a phenomenon that is supposed to prompt the repair process; however, an imbalance in this process with an altered ECM deposition results in the formation of fibrosis [133]. Various factors, including TGF-β1, promote the development of myofibroblasts by involving different microRNA (miRNA) [156] or the Src family of kinases [157]. Therefore, a promising strategy to counteract PF progression might be attenuating the differentiation of fibroblasts into myofibroblasts and limiting collagen deposition.

Oxidative stress is another important player in PF development; indeed, excessive amounts of ROS are generated during disease development [21]. Since a large amount of O_2 exchange takes place in the lungs, they are considered an organ vulnerable to oxidative stress and its associated phenomena, which can lead to apoptotic epithelial cells, increased secretion of profibrotic factors, and an increase in the differentiation of fibroblasts into myofibroblasts [78,79,81,82,103,107,158]. A great body of literature supports the involvement of epigenetics in the pathogenesis of IPF; however, studies examining the correlation between epigenetics and CTD-ILD are limited [21]. The association between a number of genetic loci and the risk of developing CTD-ILD was established by a high throughput genetic analysis [159–161]. It has been shown that rare pathogenic mutations in the telomere maintenance genes are associated with PF. Indeed, Newton *et al*. (2016) [162] demonstrated that ILD patients with rare telomere-related variants of TERT, TERC, PARN, or RTEL1 exhibited various forms of PF, which included IPF, interstitial pneumonia with autoimmune features (IPAF), and CTD-ILD. Accordingly, several studies have shown that MUC5B minor alleles correlate with a deterioration in lung function and survival rate by IPAF and CTD-ILD patients [159–161]. Similarly, exome-sequencing studies related to familial IPF revealed several mutations in TTR, RTL1, PARN, or SFTPC in RA-ILD patients, suggesting that IPF-linked genes contribute to RA-ILD susceptibility [163]. Furthermore, accumulated evidence has also shown that several genetic loci are associated with SSc-ILD susceptibility, including CTGF (also known as CCN2, which encodes the connective tissue growth factor), CD247, and IRF5 [164–167]. Other PF-associated epigenetic mechanisms include the involvement of DNA methylation, post-translational histone modification, non-coding RNA (ncRNA), miRNAs, and DNA methylation-influenced regulatory sites of genes involved in IPF [168,169]. Another interesting aspect relates to the studies on histone modifications, which revealed the involvement of epithelial-mesenchymal transition (EMT), apoptosis, and the prostaglandin E2 pathway [170]. Interestingly, histone deacetylase inhibitors were found to counteract the TGF-β1-induced differentiation of fibroblasts into myofibroblasts, the restoration of surfactant protein-C expression in AEC2, and mitigate bleomycin-induced PF [171,172]. A correct and timely diagnosis of PF within CTD-ILD and the degree to which it has progressed are necessary for establishing the appropriate therapy. Indeed, individualized treatments for each patient alongside the use of glucocorticoids (GC) and immunosuppressive agents depend on the primary disease, systemic activity, reversibility, and ILD clinical course [173,174]. For instance, when the disease reaches the chronicity phase, high-dose GC and immunosuppressive therapy may not be efficient; thus, anti-PF treatments may be applied, such as pirfenidone and nintedanib [175–177]. Interestingly, previously reported data indicated that these two drugs possess antioxidant activity, which may form the basis of their therapeutic effect [81,82]. Notably, nintedanib has been approved by the United States FDA for use in CTD-ILD with a PF-ILD phenotype alongside SSc-ILD as an inhibitor of multiple tyrosine kinases [178,179]. When the disease reaches its end stages or during its refractory cases, two promising novel therapeutic strategies have been proposed: autologous hematopoietic stem-cell transplantation and lung transplantation [180].

Based on the previous PF presentation, the pathogenesis of diseases, such as ILDs and CTD-ILD, is believed to be tightly linked to fibrosis. However, it is largely accepted that the impairment of inflammatory-associated pathways is the primary molecular mechanism that promotes profibrotic cascades and leads to aberrant tissue remodeling and fibrogenesis [181]. Nonetheless, conventional treatments are not always efficient in reversing PF progression and provoke multiple side effects; hence, alternative therapies are necessary for controlling the patient's symptoms and ameliorating their quality of life [182]. The promising anti-PF roles for natural compounds have increasingly attracted the interest of scientists over the last two decades. Indeed, natural compounds encompass multiple biological properties and potent safety standards, which are pivotal in PF prevention and treatment [183]. Interestingly, natural product-based treatments have demonstrated promising outcomes in PF management, with studies demonstrating that natural products can exert antifibrotic effects by inhibiting inflammation, oxidative stress, endothelial mesenchymal transition (EndMT), and counteracting TGF-β-mediated profibrotic cell signaling [13,184].

6. Effect and Molecular Targets of Resveratrol on PF

In addition to its antioxidant, anti-inflammatory, antiapoptotic, and anticancer effects, resveratrol was found to exert preventive and therapeutic effects on PF by impacting signaling pathways specifically implicated in PF-associated pathologies. Indeed, the inhibition of fibrogenic events such as TGF-β-mediated cell signaling and EndMT underpin the antifibrotic properties of resveratrol on PF attenuation (Fig. 4).

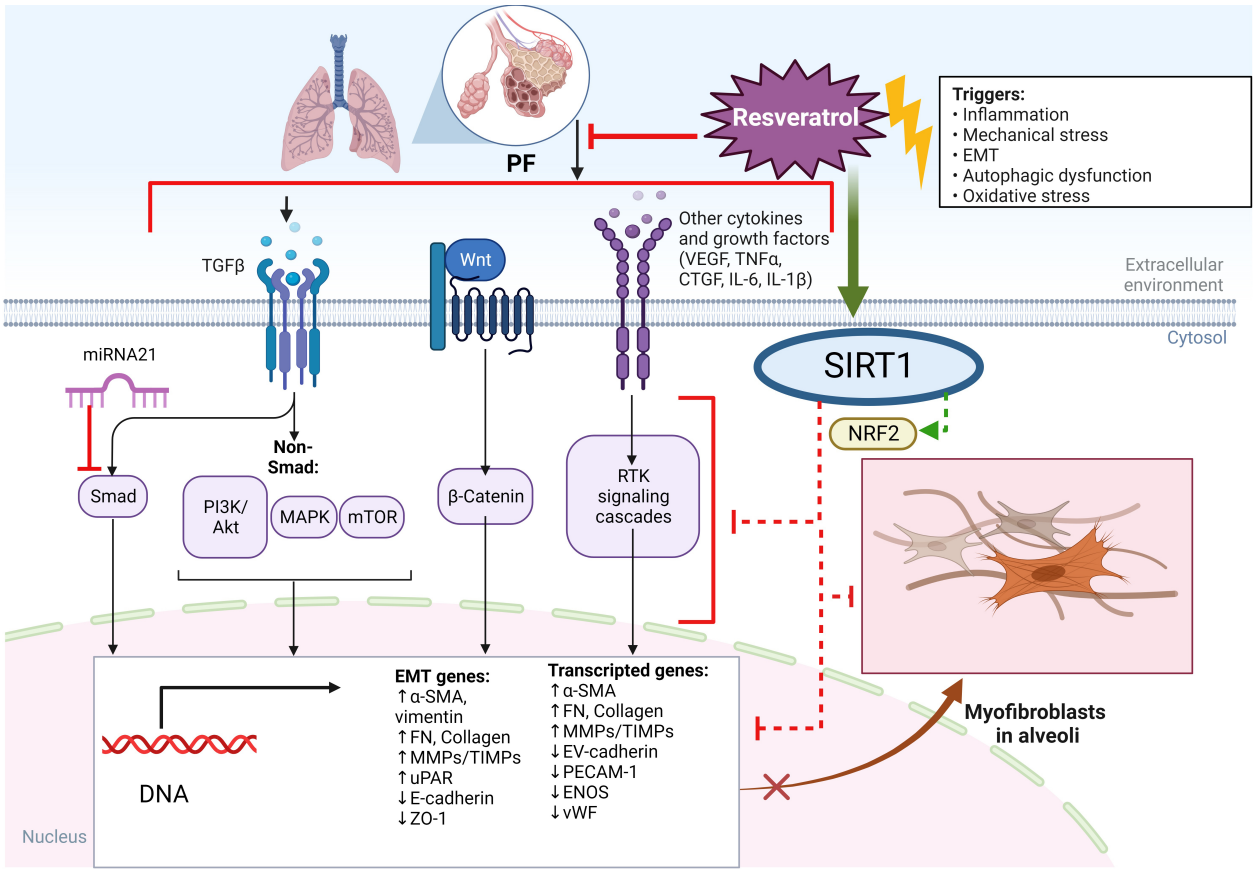

Fig. 4. Molecular targets underpinning the antifibrotic effects of resveratrol in lungs. PF, Pulmonary fibrosis; EMT, epithelial mesenchymal transition; Nrf2, the nuclear factor (erythroid-derived 2)-like 2; SIRT1, sirtuin-1; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin; IL-6, interleukin-6.

6.1 EMT Molecular Events and Myofibroblast Differentiation Inhibition

PF is associated with differentiating fibroblasts into myofibroblasts, aberrant ECM deposition, and parenchymal disorganization, all of which, ultimately, affect lung biomechanical parameters [185]. EMT is a process during which epithelial cells lose apical-basal polarity and adhesion and undergo a transition into mesenchymal cells, which potentially leads to PF formation [186,187].

Resveratrol has shown antifibrotic effects in multiple tissues and organs, including vessels, kidneys, and livers. As for the lung, resveratrol was found to alleviate fibrotic-associated pathological changes. Interestingly, by inhibiting the profibrogenic cytokine TGF- β1, which is recognized as the pivotal enhancer of EMT-associated α–SMA fiber depositions. Moreover, resveratrol also counteracts both fibroblast proliferation and their differentiation into myofibroblasts, which are two critical stages in the lung fibrotic process [188].

6.2 SIRT1 Activation

TGF-β1-induced EMT is primarily triggered by ERK 1/2 and Akt stimulation, and the subsequent activation of their downstream mediators, Smads [102], which are SIRT1-regulated targets that are responsible for E-cadherin, collagen I, and α–SMA expression [110,189–192]. Resveratrol was also shown to alleviate PF by inhibiting TAK1, which is a TGF-β-activated kinase that participates in fibroblast proliferation, collagen deposition, and scar formation [193]. SIRT1 was also demonstrated to stimulate AMPK expression in the presence of moderate resveratrol concentrations, thereby suggesting that resveratrol-induced SIRT1 may serve as a therapeutic target in the treatment of ILD diseases [194]. SIRT1/p53-activated signals have been reported to be involved in the pathogenesis of ILDs by inducing AEC2 senescence [195]. Thus, resveratrol treatment has been reported to maintain AEC2 integrity by activating SIRT1 expression, promoting p53 destabilization, and stimulating Akt and MDM2 (an oncoprotein) phosphorylation [195]. As demonstrated in neonatal rats, resveratrol acts in hyperoxia-induced lung injuries by modulating the antioxidant and anti-inflammatory hallmarks [196]. In this regard, SIRT1 has been shown to be able to control ROS levels and modulate ROS-associated cellular activities [197]. In human lung AECs, resveratrol upregulates SIRT1, which ameliorates mitochondrial membrane poten-

tial, decreases ROS levels, and reduces apoptosis, to ultimately decrease hyperoxia-induced cell damage [198].

6.3 Nrf2 Pathway Activation

The activation of various Nrf2 downstream signaling targets, such as NAD(P)H quinone dehydrogenase 1 (HO-1/NQO1), NADPH oxidase 4 (NOX4), and GSH, via several Nrf2-induced mechanisms, has been shown to promote potent antifibrotic effects and significantly attenuate PF, both *in vivo* and *in vitro*, by counteracting inflammation, oxidative stress, fibroblast–myofibroblast differentiations, and EMT [199]. Consonantly with these findings, resveratrol was found to exert a protective effect on PF by reducing systemic oxidative and nitrosative stress through the activation of AMPK- and Nrf2-associated antioxidant defense mechanisms [200,201].

The potential therapeutic and preventive effects of resveratrol are believed to both decelerate ILD and indirectly inhibit the progression of autoimmune-related ILD via the same molecular mechanisms and pathways [202].

7. Resveratrol Effect in Rheumatoid Arthritis Associated with Interstitial Lung Disease (RA-ILD)

RA-ILD is one of the leading causes of interstitial fibrosis and pulmonary failure and occurs from a complication of RA. RA is a common autoimmune disease that causes progressive articular damage, functional loss, and comorbidities; thus, presenting ILD as one of its most common extra-articular manifestations [203]. Autophagy is a self-digestion process that occurs in eukaryotic cells and mediates several intracellular biological functions, such as the removal of cytoplasmic material [204]. Autophagy plays a pivotal role in maintaining lung tissue metabolic homeostasis as well as in the occurrence and progression of chronic lung diseases owing to its role in the regulation of several respiratory tract biological functions, including inflammatory response, DNA damage repair, cell apoptosis, and cell proliferation and differentiation [205,206]. Under specific circumstances, autophagy may occur in autophagosomes, which when combined with lysosomes leads to the formation of autophagolysosomes. Moreover, autophagolysosome-associated degradation of some junction proteins, such as P62, leads to the disruption of homeostasis-associated cellular signals and metabolic pathways that are involved in several metabolic disorders [207]. In this regard, evidence supporting the connection between autophagy and ILD, further, demonstrated that resveratrol can improve RA progression through autophagy regulation. Thus, resveratrol can potentially attenuate PF by ameliorating the autophagic flux and modulating the autophagy–lysosome pathways [28]. Among the signal transduction pathways implicated in RA onset and progression, IL-6 predominantly activates the Janus kinase/signal transducers and activators of the transcription (JAK/STAT) pathway [208]. JAK/STAT has been found to be involved in PF pathogenesis [209], and its downregulation is believed to prevent the development of RA [208].

The receptor activator of nuclear factor kappa-β ligand (RANKL), also known as tumor necrosis factor ligand superfamily member 11 (TNFSF11), is one of the major JAK/STAT signaling pathway outputs and is reported to be the key mediator in arthritis-associated bone loss [210]. In this regard, resveratrol was found to interfere with the JAK/STAT/RANKL signaling pathway and significantly ameliorate lung disease by preventing the production of proinflammatory cytokines in RA-ILD rodents [211].

The activation of SIRT1 and its downstream pathways has been highlighted as a common molecular pathway that underpins the resveratrol therapeutic effects on RA and ILD. Overall, the activation of SIRT1 and its downstream pathways can downregulate the NF-κB signaling pathway and the production of several related monocyte inflammatory factors, such as TNF-α, IL-1b, IL-6, and Ki-67, which act as anti-inflammatory molecules and attenuate the RA severity [212]. The excessive production of intermembrane metalloproteinases (IMMPs) is another mechanism that promotes RA-associated EMC remodeling. In fact, the overproduction of IMMPs was found to be responsible for histological barrier impairment in fibroblast-like synoviocytes (FLS) cells and was characterized by a severe degradation of ECM proteins, FLS migration, and invasion, along with articular bones and cartilages destruction [213–215]. SIRT1 activation was also found to suppress RA progression by promoting the decomposition of MMPs and counteracting FLS invasion [216].

The Nrf2– Kelch-like ECH-associated protein 1 (Keap1) pathway is recognized as playing a key role in resveratrol-mediated antioxidant activity [217]. Under physiological conditions, Nrf2 is found sequestered in the cytoplasm in its inactive form, which is bound to Keap1 [218–220]. In response to appropriate stimuli, the conformation of Keap1 is modified, which releases Nrf2 to complex with the small Maf (sMaf) protein. The Nrf2–sMaf protein complex, then, translocates into the nucleus and binds to DNA-contained antioxidant response elements (AREs), which promotes the expression of heme oxygenase-1 (HO-1), and exerts antioxidant protective effects [221–223]. Resveratrol was found to promote Nrf2 and HO-1 expression, while downregulating the expression of Keap1 which reduced ROS and malonaldehyde (MDA) generation, and inhibited NF-κB–p65 activation, and FLS proliferation and migration [217]. NF-κB was also shown to negatively regulate the expressions of miR-29a-3p and miR-23a-3p, the miRNAs responsible for activating Keap1, which directly targets Cullin3 (CUL3), an essential regulator of Nrf2 ubiquitination and degradation [224]. In this context, it was proven that resveratrol ameliorated RA by activating the Nrf2-ARE signaling pathway via the SIRT1/NF-κB/miR-29a-3p/Keap1 and SIRT1/NF-

κB/miR-23a-3p/CUL3 cascades [224]. The resveratrol-mediated blockage of the previous pathway is also believed to inhibit the ROS-mediated MAPK activation and promote the whole cascade that leads to the activation of both activator protein-1 (AP-1) and NF-κB; hence, forming a complex network of signals that are all interconnected by the SIRT1 pathway [225].

8. Resveratrol Effect in Associated Systemic Sclerosis with Interstitial Lung Disease (SSc-ILD)

Systemic sclerosis (SSc), also referred to as scleroderma, is a rare autoimmune disease that is associated with vasculopathy and characterized by microvascular damage, innate and adaptive immune dysfunction, and fibrosis of the skin and/or internal organs [77–80]. ILD is a common complication and the leading cause of death in SSc patients and is often linked to pulmonary hypertension (PH) [226]. Although there is a paucity of studies investigating the effect of resveratrol on SSc-associated PF, recently, it has been reported that resveratrol could counteract SSc-related PF by suppressing proinflammatory and profibrotic processes, including cell proliferation and fibroblast differentiation, via a SIRT1-mediated inhibition of the TGF-β pathway [227]. Furthermore, the serine/threonine protein kinase, mammalian target of rapamycin (mTOR) has been reported to initiate PF-associated fibrotic events [228]. Moreover, Yao *et al*. (2020) [227] demonstrated that a resveratrol-dependent overexpression of SIRT1 suppressed mTOR expression and ameliorated fibrosis and inflammation, thereby suggesting that the downregulation of mTOR by SIRT1 underpins the resveratrol therapeutic effect on SSc-associated PF. Additionally, in the same study, a meta-analysis of the genes associated with the biological properties of resveratrol illustrated the involvement of 79 pathways, which contained genes targeted by resveratrol, 27 of which were concomitantly involved in SSc [227].

9. Resveratrol Effect in Schrödinger's Syndrome with Interstitial Lung Disease (SS-ILD)

ILD is considered the most frequent and severe pulmonary complication in primary Sjögren's syndrome (SS), with significant morbidity and mortality. Although ILD was described as a late manifestation of SS, recent studies have demonstrated that between 10 and 51% of patients might develop ILD years before the onset of SS [229]. Resveratrol was shown to improve SS by enhancing SIRT1 activity and the expression of IL-10. Thus, the therapeutic effect of resveratrol on SS-associated salivary dysfunction appears to be mediated by a SIRT1-like activity, which is known to block NF-κB nuclear translocation by inhibiting IkappaB kinase (IKK) [230], yet little is known about the effect of resveratrol on SS as an autoimmune disease. Thus, more studies are required to identify the molecular mechanisms through which resveratrol affects both SS and SS-ILD.

10. Resveratrol Effect in Pulmonary Hypertension PH-ILD

The development of pulmonary hypertension (PH) as a secondary ailment to PF (PF-PH) is the primary factor in the mortality and morbidity of the disease [231]. The high prevalence of PH in PF patients is very worrisome since it presents a significant predictor of mortality [231]. Until recently, PH was thought to be solely provoked by fibrosis-mediated lung parenchyma destruction, which leads to hypoxic vasoconstriction, severe pulmonary vascular remodeling, loss of vascular bed density, and elevation in pulmonary pressure [232]. The increase in pulmonary pressure is maintained, at least in part, by sustained inflammation, oxidative stress, and dysfunction in endothelial cells (ECs) proliferation and angiogenesis as well as ECs- and vascular smooth muscle cells (VSMCs)-mediated ECM remodeling [77–80]. This aberrant vascular remodeling occurs in all types of vessels within the pulmonary vascular tree, with ECs and VSMCs the most prominently involved vascular cells [77–80]. However, it has been recently demonstrated that there is no significant correlation between fibrosis severity and the development of PH [232]. Indeed, relevant histological and molecular differences between PF and PF-PH patients have recently been identified and have helped to deviate from this paradigm [233–236]. Interestingly, the systemic and cardiac vasculature therapeutic properties of resveratrol may also target pulmonary hypertensive disease mediators, including the antifibrotic pathways [237]. In this regard, resveratrol was shown to protect against pulmonary artery hypertension (PAH), via chemoprotective [95], anti-inflammatory, antioxidant [238], antiproliferative [239], and antiapoptotic mechanisms [240]. Specifically, resveratrol alleviates hyperoxia-induced histological lung injury, regulates redox unbalance, decreases proinflammatory cytokines, and downregulates fibrosis-associated protein expression [241].

The Wnt/beta-catenin signaling pathway not only mediates cell differentiation in the early stages of lung development, yet also participates in the organization of the lung tissue structure. In fact, Wnt signaling expression was shown to be impaired in the lungs of IPF patients [242,243]. Accordingly, recent studies demonstrated that the inhibition of glycogen synthase kinase (GSK)-3β, a negative regulator of the Wnt/β-catenin signaling pathway [244], mediated the downregulation of the Wnt/β-catenin signaling expression in hyperoxia [245]. Wnt signaling also regulates the trans-differentiation of stem cell-like alveolar epithelial type 2 cells (ACE29) to type 1 epithelial cells (ACE1) [246]. Specifically, a study suggested that resveratrol could exert protective effects against PF by promoting the trans-differentiation of ACE2 into ACE1 through inhibiting the

Wnt/β-catenin-associated signals, thereby effectively attenuating hyperoxia-induced oxidative stress, the inflammatory responses, and PF [241]. The same study also indicated that resveratrol could inhibit the Wnt/β-catenin signaling pathway by diminishing the expressions of lymphoid enhancer factor-1, Wnt-induced signaling protein-1, and cyclin D1 [241].

11. Resveratrol Effect in Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease, which is characterized by the production of autoantibodies and presents a complex pathogenesis that is triggered by both environmental factors and genetic predisposition [247,248]. The early stages of SLE are associated with the impaired clearance of apoptotic cells by macrophages, which leads to an altered autoimmune response, characterized by the hyperactivation of T cells, a shift from Th1 to Th2, increased IL-10 levels, activation of B cells, and the excessive generation of autoantibodies [249,250]. This altered response can cause damage to the peripheral tissue blood vessels, vasculopathy, and vasculitis, which are common aspects in SLE patients that lead to cardiovascular and renal damage [251–253]. In this context, resveratrol was shown to attenuate proteinuria, decrease IgM/IgG kidney deposition, and reduce kidney histological lesions [254]. Authors also reported that resveratrol alleviated the altered autoimmune response, T cells/B cells activation, the proliferation profile [254], Th1/Th2 ratio, and Th1 cytokine-promoted immunoglobulins release by acting in a SIRT1-mediated fashion [254]. Conversely, resveratrol enhanced the apoptosis of T cells, either by acting through Fas, BCL-2, Bax, or p53-mediated pathways, or through a mechanism involving the depolarization of mitochondrial membranes and caspase activation [29,255–257]. Ultimately, both methods alleviated the impaired apoptosis, which characterizes the SLE autoimmune response. Additionally, the activation of SIRT1 by resveratrol was found to inhibit COX2 expression by suppressing both NF-kB activation and TNF-α-induced inflammation in fibroblasts [29,255–257]. Resveratrol also appeared to potentially delay SLE-induced atherogenesis progression and SLE-associated kidney and heart failures by normalizing cholesterol levels [258]. In contrast, the lack of data regarding the use of resveratrol in other common SLE complications, such as lung impairment, might be a solid motive for performing more clinical trials to better understand its molecular mechanism in attenuating these ILD-related pathologies. Given these findings, it is hard to suggest resveratrol as a curative drug for SLE; however, it should be considered a promising supplement in managing SLE therapy [128].

PF may co-occur in other pathologies than the previously mentioned autoimmune diseases. Indeed, an important number of PF and lung cancer patients were infected with COVID-19 during the virus pandemic. As featured diseases of PF, they are known to cause high morbidity and mortality rates worldwide [259]. Therefore, a significant body of data has been generated by investigating the effects of resveratrol on lung cancer and COVID-19 infections by targeting PF as a component.

12. Resveratrol Effect in Other PF-Associated Pathologies

12.1 COVID-19-Associated PF

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged viral pathogen that causes coronavirus disease-2019 (COVID-19) [260]. SARS-CoV-2 belongs to a family of coronaviruses, which are enveloped and segmented RNA viruses [261]. The rapid rate of transmission and infectivity of this viral disease resides in the fact that the SARS-CoV-2 protein is cleaved by many serine proteases [23]. Interestingly, IPF patients and patients with severe post-COVID-19 infection-PF manifest similar pathological characteristics [23]. Since AEC2 and alveolar macrophages are essential regulators in PF promotion, their altered physiology due to COVID-19 infection may cause PF as a sequela of the disease [23]. SARS-CoV-2 potentially infects epithelial cells, AEC2, alveolar macrophages, intestinal enterocytes, and eventually the basal epithelial cells in the nasal passages [23,261,262]. COVID-19 patients have increased levels of IFN-γ, TGF-β, IL-17, and IL-8, compared to a normal cytokine profile, which correlates to an excessive Th1 response and a profibrotic inflammatory profile [261,262]. Additionally, high levels of TGF-β suggest increased ECM deposition and enhanced fibroblast to myofibroblast differentiation [23,262]. An increase in IL-17 was also demonstrated during COVID-associated PF resulting in neutrophil degranulation, high oxidative stress, and fibrotic deposition in the lungs [263]. These pathological conditions are similar to those in IPF-associated PF and might occur in the longer term to eventually promote COVID-19-associated PF [23]. In this regard, resveratrol was proposed as an anti-covid agent because it was shown to act as an antiviral alongside its role in the immune stimulation, downregulation of proinflammatory cytokine release, and reduction in oxidative stress-associated lung injury [16,264]. *In silico* studies showed that resveratrol has a high affinity for the COVID-19 S1 spike protein [265]. It is also strongly believed that resveratrol counteracts COVID-19 viral infection through its ability to inhibit several infection-associated features, such as the transcription of the viral proteases Mpro and PL-pro [266–269], the polymerase activity of RNA-dependent RNA [270], the release of proinflammatory cytokines [271, 272], the aggregation of platelets [273,274], the synthesis of endothelial nitric oxide [275–277], the activation of proinflammatory NF-kB [278], and the activation of proinflammatory Th-17 T cells [279]. Within the COVID-19 setting, resveratrol has also been reported to promote antioxidant and anti-inflammatory effects by stimulating the production of glutathione in lung epithelium cells [280–282] and sup-

pressing the bradykinin-induced COX-2/PGE2 production, in a SIRT1-dependent way [283]. The ability to counteract and/or ameliorate COVID-19-associated hemostatic disorders has also been reported as part of the resveratrol therapeutic potential against COVID-19 [16].

12.2 Effect of Resveratrol in Lung Cancer-Associated with Pulmonary Fibrosis (LC-PF)

PF patients manifest chronic progressive and diffuse fibrotic lung disease. This persistent inflammatory state, along with the repeated fibrotic scars, has been linked to the etiologies of various neoplasms, including lung cancer [83,113]. In this regard, studies demonstrated an increased estimated risk of lung cancer in ILD patients of between 7 and 14 times [284]. Interestingly, lung tumors in IPF patients develop preferentially in the peripheral adjacent zones to fibrotic areas and present different histologic distributions and immunohistochemical characteristics compared to non-IPF-associated lung tumors [24,25]. Furthermore, studies have indicated that IPF and lung cancer share many pathogenic features, including genetic and epigenetic mechanisms [24,25]. Indeed, genetic and epigenetic impairments lead to the abnormal activation of common transduction pathways, such as Wnt/β-catenin and phosphoinositide 3-kinase/protein kinase B, which mediate the metaplasia and hyperproliferation of AEC2. Such an aspect represents a common thread between carcinogenesis and ILD, which might even lead to the use of similar drugs [25].

These alterations are also believed to be age-related and may result in deregulated gene expression, increased oxidative stress, and the accumulation of dysfunctional organelles, ultimately resulting in the development of lung diseases, including cancer. Resveratrol has been reported to positively impact lifespan regulations, health maintenance, and age-associated disorders [285]. Additionally, resveratrol administration appears to be a potential method for slowing the aging-related decline in lung function and structure by maintaining the integrity of AEC2 [195]. In lung cancer cells, resveratrol acts as an inhibitor of the epithelial growth factor receptor EGFR [286,287], mTOR [286,288], and Akt [289–291]. Moreover, in addition to the GLUT1 glucose transporter, resveratrol has been reported to inhibit the NF-κB [126,290,292] and JAK/STAT pathways [292]. Alternatively, resveratrol has been demonstrated to activate the p53 tumor suppressor [289,291] and increase caspase activation [286,292], thereby orienting cancer cells toward apoptosis. As indicated in previous sections of this paper, resveratrol is a well-established SIRT1 activator [293,294]. Notably, resveratrol-induced SIRT1 activation resulted in a SIRT1-mediated decrease in NF-κB activation in cancer cells [26,27].

Accumulated data have also shown that resveratrol amplifies the effects of lung cancer chemotherapy drugs, by increasing their intracellular concentrations and triggering apoptosis, autophagy, and senescence [287]. Additionally, resveratrol can interact with other chemotherapeutic drugs to induce and/or potentiate their antitumor effects and, in some cases, abolish chemotherapeutic drug resistance [295,296].

Given the diverse resveratrol effects, this compound was subjected to increasing multidisciplinary studies aiming to highlight its therapeutic prospect in ILD and CTD-ILD.

13. Studies on Resveratrol Effects in PF and Related Pathologies

Research on the potential therapeutic effects of resveratrol in ILDs is ongoing, and although the results are still preliminary, there is evidence that suggests it may have beneficial effects. In animal studies, resveratrol has been shown to reduce the key features in ILDs, such as lung inflammation and fibrosis. Additionally, some studies have found that resveratrol can improve lung function in patients with ILDs.

13.1 In Silico Studies

Despite the compelling data highlighting the therapeutic potential of resveratrol, *in silico* studies remain limited. A resveratrol-targeted genes interaction network analysis established using both STITCH and the Kyoto Encyclopedia of Genes and Genomes (KEGG) database has shown that 79 genes were included in the pathways associated with the therapeutic effects of resveratrol in SSc [227]. The study focused on the SIRT1/mTOR signaling pathway as one of the crucial regulatory components, previously suggested to alleviate inflammation and fibrosis [227]. Another study on *Polygonum cuspidatum*, a resveratrol-contained plant, found that it exhibited excellent inhibitory activity of TGF-β receptor type I (RI) at a dose of 2.211 µM. Moreover, molecular docking studies showed the establishment of hydrogen bonds at HID_283 and GLU_245, which could be considered the active sites underpinning the interactions between resveratrol and TGF-β RI. The study suggests that the potential inhibitory effect of resveratrol is a promising lead for developing TGF-β RI inhibitors in the future [297] (Table 2).

13.2 In Vitro Studies

Extensive data have confirmed the role of oxidative stress in the onset and development of PF [78–82,103,311]. In particular, several studies concluded that the SIRT1-mediated protective effect against oxidative stress and inflammation by resveratrol played an important role in regulating several pathways implicated in PF-associated pathologies [293]. For instance, a dose of 50 µM resveratrol activated SIRT1 and protected the lungs against bleomycin-induced inflammation and fibrosis [30]. In A549 cells, which are used as a model of human AEC2, treatment with resveratrol (10 µM) protected against cigarette smoke-

Table 2. Resveratrol effect in CTD-ILDs experimental models (*in silico*, *in vitro*, and *in vivo* studies).

Model	Type of cell/rodent	Dose	Major results	Reference
In vitro	BEAS-2B, WI38-VA13, and Raw264.7	30 mg/kg; 10 μM	Activation of AMPK and Nrf2-associated antioxidant defense mechanisms	[196,197]
	C57BL/6 female mice	50 μM	SIRT1 activation, ↓ collagen production, and ↓ TNF-α overexpression	[30]
	A549 cells	10 μM	Activation of Nrf2 and ↑ glutathione synthesis	[99]
	HPAEpiCs	50 μM	Activation of JNK1/2 /p38 MAPK, via the c-Src/PDGFR pathway, ↑ VCAM-1 expression, and ↓ H_2O_2-induced oxidative stress	[197]
	U937 cells	10–50 μM	Inhibition of PI3K and VEGF functions	[298,299]
	HUVECs	10 μM	SIRT1-mediated mTOR degradation	[300]
	MCF-7 cells	50 μM	↓ phosphorylation of PRAS40T246 and PRAS40S183 and increased binding of PRAS40 to RAPTOR/TORC1	[301]
In vivo	Mice	15–60 mg/kg	Activation of AMPK and Nrf2-associated antioxidant defense mechanisms	[196,197]
	Mice		↓ associated pathological changes: weight loss and reduced mortality rates	[102]
	C57BL/6 mice	20 mg/kg	↓ myofibroblast differentiation and ECM expression	[302]
	Wistar albinos	10 mg/kg	↓ proinflammatory cytokine levels, including TNF-α, TGF-β, IL-1b, and IL-6, and ↓ MDA	[303]
	Rats	10 mg/kg	↓ fibrosis, ↓ MDA levels in lung tissue and serum, ↑ plasma antioxidant profile, and ↓ neutrophil numbers	[304]
	BALB/c mice	25–50 mg/kg	↓ MDA, ↓ protein carbonyl, ↓ total oxidant status, ↓ myeloperoxidase, ↓ oxidative stress index, ↓ hydroxyproline, and ↓ DNA damage	[305]
	Wistar male rats	10 mg/kg/day	↓ PF-induced inflammatory response, ↓ lung damage, EMT inhibition, ↓ TLR4/NF-κB, and TGF-β1/Smad3 signaling pathway expressions	[306]
	Wistar male rats	50 mg/kg	SIRT1/PGC-1α signaling pathway inhibition	[307]
	ICR male mice	0.3 mg/kg	↓ TGF-β1 levels, ↑ SOD, ↑ CAT TGF-β1/Smad2/3/4 signaling pathway suppression, LPS-induced oxidative stress, and PF	[100]
	Sprague-Dawley rats	60 mg/kg	↓ TGF-β1 and p-Smad2/3, ↑ miR-21 expression Inflammatory responses and EMT inhibition	[309]
	Bleomycin-induced lung fibrosis in mice		↓ SIRT1-mediated PF through EMT inhibition in lung tissue	[102]
	Sprague-Dawley rats	40 mg/kg	↓ TGF-β1; inhibition of Smad2/3 and ERK1/2 phosphorylation, ↓ TNF-α, ↓ IL-6, and ↓ IL-13 levels	[308]
	Bleomycin-treated mice		↑ resveratrol-mediated SIRT1 overexpression in lung epithelial cells and fibroblasts	[310]
	Bleomycin-induced PF in mice	50 μM	↑ resveratrol-mediated SIRT1 and ↓ PF features	[29]
	C57BL/6J mice	20 mg/kg	↓ inflammation and fibrosis and ↓ STAT3 activation	[111]
	ICR mice	5 mg/kg	↓ VCAM-1 protein levels, ↓ mRNA expression in mice lungs, and ↓ leucocytes in the BAL fluid	[295]
	Wistar male rats	10 mg/kg	Inhibition of JAK/STAT/RANKL signaling pathways	[207]

AMPK, AMP-activated protein kinase; JNK1/2/p38 MAPK, c-Jun N-terminal protein kinase/1/2/protein38–mitogen-activated protein kinase; a c-Src/PDGFR, proto-oncogenes tyrosine kinases/platelet-derived growth factor receptor; VCAM-1, vascular cell adhesion molecule 1; H_2O_2, hydrogen peroxide; TORC1, mammalian target of rapamycin complex-1; TGF-β, transforming growth factor-β; IL-1b, interleukin-1b; IL-13, interleukin 13; MDA, malonaldehyde; TLR4, toll-like receptor 4; ERK1/2, extracellular signal regulator kinase; miR-21, microRNA-21; STAT3, signal transducer and activator of transcription 3; mRNA, messenger RNA; BAL, bronchoscopy and bronchoalveolar lavage. JAK/STAT/RANKL/Janus kinase/signal transducers and activators of transcription RANK ligand. ↑ , increase in/upregulation of; ↓ , decrease in/downregulation of.

induced oxidative stress by activating Nrf2 and inducing glutathione synthesis [281]. Studies conducted on the human lung epithelial cell line (HPAEpiCs), reported that resveratrol (50 µM) could attenuate *Staphylococcus aureus*-induced inflammation [298] by (a) activating both JNK1/2 and p38 MAPK via the c-Src/PDGFR pathway, (b) upregulating VCAM-1 expression, and (c) attenuating H_2O_2-induced oxidative stress [299,300]. Both PI3K and VEGF have been shown to be involved in PF as part of the activated inflammatory machinery [301,312]. In this context, studies performed *in vitro* on differentiated U937 monocytes reported that resveratrol (10–50 µM) inhibited PI3K and VEGF functions, further, emphasizing these two pathways as important components in the resveratrol anti-inflammatory mechanism [312,313]. Additional *in vitro* studies emphasized the role of resveratrol in activating SIRT1-mediated mTOR degradation, which ameliorated bleomycin-induced fibrosis and inflammation [314]. A study that focused on mTOR pathway phosphoproteomics suggested that resveratrol (50 µM) inhibited autophagy in serum-deprived cells by (1) decreasing the phosphorylation of $PRAS40^{T246}$ and $PRAS40^{S183}$, two proteins that belong to the mTORC1 signaling pathway, and (2) increased the binding of PRAS40 to RAPTOR/TORC1 (Table 2) [302].

13.3 In Vivo Studies

PF is characterized by continued alveolar epithelial injury and unregulated repair, which occur through several different mechanisms, including fibroblast accumulation and differentiation and excessive ECM deposition [303]. Bleomycin is an antitumor drug that can induce PF during clinical treatment and, for this reason, has been used as means to artificially induce PF in animal models [304]. Here, resveratrol was shown to counteract weight loss and reduce the mortality rate in a bleomycin-induced mouse model of lung fibrosis [192]. Another fibrosis hallmark is the differentiation of fibroblasts into myofibroblasts [305]. In this context, resveratrol was shown to decrease fibroblast differentiation and ECM deposition, thereby alleviating lung fibrosis in a mouse model of bleomycin-induced lung fibrosis [306]. In comparison to the control group, resveratrol (14 days treatment at 10 mg/kg) significantly decreased lung collagen deposition, proinflammatory cytokines secretion (TNF-α, TGF-β, IL-1b, and IL-6), and MDA levels [307] in a bleomycin-induced PF rat model [307]. Moreover, in an adult mouse model of PF, resveratrol (10 mg/kg) decreased tissue lung fibrosis and MDA serum levels, while increasing the plasma antioxidant profile. Further, in a bleomycin-induced PF mouse model, resveratrol administration (25–50 mg/kg) reduced a set of oxidative stress markers, including MDA, protein carbonylation, total oxidant status, myeloperoxidase, oxidative stress index, and DNA damage, while concomitantly increasing GSH, total antioxidant status, and SOD [308]. Similarly, in a bleomycin-induced PF rat model, resveratrol administration was able to reduce both the PF-induced inflammatory response and lung damage by inhibiting EMT and downregulating TLR4/NF-κB and TGF-β1/Smad3 signaling pathways [309]. To assess the resveratrol protective effects on inflammation-elicited PF, Wang *et al*. (2017) [310] induced lipopolysaccharide (LPS)- and cigarette smoke (CS)-elicited inflammation and oxidative stress in the lungs of a rat model. The finding in the study indicated that resveratrol was able to inhibit the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) signaling pathway, while further experiments proved that resveratrol intake significantly increased the levels SOD, while reducing those of MDA, to ultimately promote PGC-1α mRNA expression and attenuate oxidative stress-associated effects [310].

In an LPS-induced PF mouse model, treatment with resveratrol (0.3 mg/kg) managed to downregulate TGF-β1 levels, and increase the activities of SOD and CAT by suppressing the TGF-β1/Smad2/3/4 signaling pathway, ultimately reducing LPS-induced oxidative stress and PF [102]. Another recent study demonstrated that polydatin (40 mg/kg), a resveratrol glucoside derivative, both suppressed the expression of TGF-β1 in an IPF rat model and inhibited the phosphorylation of Smad2/3 and ERK1/2, to efficiently decrease TNF-α, IL-6, and IL-13 levels. Concomitantly, an attenuation in alveoli damage, reduced inflammatory cell infiltration, and edema formation were also observed [111]. In line with the previous study, resveratrol (60 mg/kg) reduced TGF-β1 and p-Smad2/3 in a bleomycin-induced PF rat model by inducing miR-21 expression, to ultimately ameliorate PF by inhibiting both the inflammatory responses and EMT [315]. In a related study, resveratrol was also capable of ameliorating bleomycin-induced PF by inhibiting EMT and suppressing the TLR4/NF-κB and TGF-β1/Smad3 signaling pathways [309]. In a mouse model of bleomycin-induced lung injury, resveratrol promoted SIRT1-mediated PF amelioration by inhibiting EMT in lung tissues [192]. A similar study also suggested that the viability rate in animals treated with resveratrol improved and fibrotic marker levels reduced, which might be due to a resveratrol-mediated SIRT1 overexpression in lung epithelial cells and fibroblasts [316]. In their research, Chu *et al*. (2018) [30] demonstrated that resveratrol-mediated SIRT1 activation attenuated PF features in a mouse model of bleomycin-induced PF. Furthermore, a study analyzing the resveratrol effects on PF development reported that resveratrol administration (2 mg/kg) inhibited inflammation and fibrosis by preventing STAT3 activation [317].

Additionally, an increase in the atherosclerotic hallmark vascular cell adhesion molecule 1 (VCAM-1) protein and mRNA expression was observed in mice intratracheally administered with a heat-killed *Staphylococcus aureus* (HKSA) preparation. Resveratrol administration (5 mg/kg) managed to reduce the HKSA-induced increase in

VCAM-1 protein levels and mRNA expression. Notably, both the VCAM-1-neutralizing antibody and resveratrol treatment were able to reduce the HKSA-induced leucocyte infiltration in the bronchoalveolar lavage (BAL) fluid and pulmonary hematoma formation, in a similar way [299]. It was also observed that resveratrol (10 mg/kg) inhibited the JAK/STAT/RANKL signaling pathway and ameliorated RA-ILD symptoms in a rat model [211]. Moreover, further studies have also demonstrated that resveratrol can improve RA progression by regulating autophagy, a process, as previously explained, which is believed to be connected to ILD (Table 2) [28].

14. How Much do We Know about Resveratrol as a Drug Candidate?

Resveratrol is a well-known nutraceutical compound that possesses a wide range of pharmacological properties. Several clinical trials have previously highlighted this molecule as a promising therapeutic drug candidate in the treatment of many diseases [318]. In addition to its protective effects on the respiratory system, resveratrol also possesses beneficial actions against cardiovascular diseases, platelet aggregation, diabetes, and neurodegenerative diseases [319]. Indeed, resveratrol and its analogs are pharmacologically safe and can be used alongside other drugs to improve their therapeutic efficacy and reduce toxicity [318]. However, its application in the food and pharmaceutical industries is still limited, mainly due to its low bioavailability, water solubility, and chemical stability; moreover, resveratrol is easily degraded and excreted, especially in biological systems [320,321]. In the liver and the intestine, UDP-glucuronosyltransferase (UGT) rapidly degrades resveratrol to glucuronic acid and sulfate conjugations producing resveratrol-3-O-glucuronide (R3G) as the most abundant metabolite in both animal and human models [322,323]. This metabolic pathway appears to be the main factor in modulating resveratrol bioavailability [321,324]. Indeed, glucuronidation was demonstrated to reduce resveratrol permeability and increase its excretion in cells [118,322,323], while metabolites resulting from the degradation of resveratrol can become a systemic reservoir of these compounds [325].

In line with this, resveratrol is also known to be photosensitive, thermosensitive, and pH sensitive, and because of its low hydrosolubility, it requires emulsifiers or stabilizers to reach a biologically effective dosage [320,326]. Another potential issue is whether resveratrol can accumulate in target organs at suitable bioactive concentrations. Indeed, studies have proven that circulating levels of plasmatic resveratrol are barely detectable [321,327], and in most cases, resveratrol is administered in its free form, which has low solubility and, therefore, is poorly suited for its delivery in biological systems [328]. In this regard, pulmonary administration could be considered an appealing alternative to the oral administration of resveratrol since the pulmonary route may ameliorate the pharmacokinetic parameters of molecules with extensive metabolism [329]. Several research groups have attempted to ameliorate resveratrol bioavailability through its complexation with β-cyclodextrins or hydroxypropyl-β-cyclodextrins [330], or by employing new formulations, which have included solid dispersion [331], liposomes [332], and lipid or polymeric nanoparticles [328,333]. In particular, Trotta *et al*. (2015) [334] formulated resveratrol as a spray-dried powder for inhalation, which was found to exert a significant antioxidant and anti-inflammatory effect in Calu 2 pulmonary epithelial cells. Moreover, in an acute lung injury animal model, inhaled resveratrol loaded on cholesterol-conjugated polyamidoamine (PAM-Chol) was able to decrease proinflammatory cytokine levels, thereby indicating the potential therapeutic effect of this resveratrol formulation [335]. Concurrently, another study investigated and confirmed the feasibility of resveratrol pulmonary route delivery to improve its bioavailability by avoiding first-pass metabolism and depositing significant amounts at lung disease sites of action. In this study, the resveratrol/hydroxypropyl-β-cyclodextrin (HP-β-CD) inclusion complex was used as an inhaled resveratrol formulation to resolve the previous solubility issues since HP-β-CD was proven to enhance the hydrophilicity of drugs with low solubility [329]. These findings strongly emphasize the feasibility of resveratrol pulmonary administration, although some limitations, including excipient amounts and efficiencies, and pharmacodynamics, still need to be resolved [329]. Therefore, new resveratrol formulations are needed to improve its bioavailability and target specific organs. Moreover, resveratrol combinations with conventional chemotherapeutic preparations have been proven efficient, especially in tumor treatment [336], thereby highlighting novel ways to use these drug formulations.

15. Conclusion and Future Perspectives

Based on the data presented in this review, a large body of evidence supports the multifaceted and quite bountiful benefits of resveratrol on PF. Resveratrol can exert its lung antifibrotic action through more classical effects, such as scavenging free radicals, modulating antioxidant enzymes, and inhibiting inflammatory-associated signaling pathways, as well as by modulating closely associated PF molecular targets, including SIRT, Nrf2, and EMT. The data gathered and discussed here indicate that the reported resveratrol benefits are not only disease-preventive but also disease-ameliorative; thus, it would not be surprising if this nutraceutical becomes more adopted into the routine management of PF patients or those at high risks of similar fibrotic diseases. In fact, despite some challenges involving the adverse effects and poor bioavailability of resveratrol, various efforts have been put forward to mitigate these issues, and indeed, much improvement has been achieved during the past decade by employing new resver-

atrol formulations, which have been specifically adapted for lung-associated pathologies. Nonetheless, future challenges should be directed to performing long-term clinical trials on PF patients using well-determined resveratrol concentrations to possibly reinforce and prove resveratrol's protective and/or therapeutic role. Indeed, *in vitro* and *in vivo* concentration ranges of biologically active resveratrol differ significantly; thus, based on the available data, it is difficult to extrapolate the most beneficial resveratrol dosage with which to avoid potential toxicity in humans [12]. A more critical aspect of that mentioned above is the dose-dependent hormetic behavior of resveratrol, which tightly determines whether the final biological outcome is positive or negative [337–339]. Moreover, the interaction between resveratrol and the body's redox state also affects its final effect [340–342]. Furthermore, to improve the poor bioavailability attached to resveratrol, new lung-oriented formulations with better absorption and pharmacodynamics need to be developed and commercialized. All the aforementioned factors might explain many of the controversial results associated with resveratrol that are found in the literature; therefore, a more comprehensive and systematic investigation is needed to further define the therapeutic potential of resveratrol. In conclusion, we firmly believe resveratrol could be helpful in fighting PF and associated fibrotic conditions; therefore, more pharmacological and clinical studies should be conducted to better determine its safety, dosages, and efficacy.

Author Contributions

IR, TC, AMP, RG, HZ, AHE, and GP participated in the manuscript conceptualization, original draft preparation, review, and editing of the final version. GP was responsible for the project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Given his role as Editor, Gianfranco Pintus had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Md Soriful Islam.

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