Goji Berry as a Therapeutic Candidate in Age-Associated Pulmonary Fibrosis: Insights into Collagen Regulation and Fibrotic Mechanisms

ABSTRACT

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| **Introduction**: Pulmonary fibrosis (PF) is a progressive lung disorder marked by excessive collagen accumulation and tissue remodeling, commonly associated with aging and oxidative stress. Goji berry (Lycium barbarum), a natural source of bioactive compounds such as Lycium barbarum polysaccharides (LBP), has demonstrated potential in mitigating oxidative lung damage and fibrotic changes due to its potent antioxidant and anti-inflammatory properties. This review examines the molecular mechanisms through which Goji berry may help regulate oxidative stress, inflammation, and fibrosis in pulmonary tissues.  **Methods**: A narrative literature review was conducted by systematically searching databases including Google Scholar, PubMed, ScienceDirect, and SpringerLink for studies published between 2004 and 2024. Eligible studies were selected based on predefined criteria, focusing on in vivo models that evaluated the effects of Goji berry or LBP on pulmonary oxidative injury, inflammation, and fibrosis.  **Results and Discussion**: Three key studies were analyzed. In aged mice, LBP (200–400 mg/kg/day) enhanced lung antioxidant enzyme levels (e.g., SOD, GPx) and significantly reduced markers of oxidative damage (e.g., MDA). In exercise-induced oxidative models, LBP (up to 300 mg/kg/day) improved antioxidant enzyme activity and lowered malondialdehyde (MDA), a marker of lipid peroxidation. Most notably, in a cigarette smoke-induced lung injury model, LBP (100–200 mg/kg/day) reduced TNF-α, IL-6, and IL-8, inhibited NF-κB signaling, and improved lung histology, demonstrating its potential to counteract both oxidative stress and inflammation. Across studies, Goji berry’s polysaccharides consistently demonstrated antioxidant, anti-inflammatory, and collagen-modulating effects that mitigated pulmonary fibrotic changes. Additionally, Goji berry's ability to reduce TGF-β and modulate fibrogenic signaling pathways offers a potential alternative or complementary strategy to current therapies like pirfenidone and nintedanib, which primarily target fibroblast activity but do not address the underlying oxidative damage.  **Conclusion**: Goji berry, through its bioactive compound LBP, presents a promising natural therapeutic agent for managing pulmonary fibrosis. Its capacity to modulate oxidative stress, inflammation, and collagen deposition highlights its potential in reducing lung damage caused by aging or environmental exposure. However, further clinical validation and exploration into its synergistic effects with current therapies are warranted to establish its role in fibrosis treatment and its broader applicability in lung health. Future research should focus on large-scale clinical trials, optimizing dosing regimens, and assessing long-term safety and efficacy in human populations**.** |

*Keywords: Goji berry, Lycium barbarum, pulmonary fibrosis, oxidative stress, antioxidant therapy*

1. INTRODUCTION

Pulmonary fibrosis is a progressive and often irreversible condition characterized by excessive accumulation of extracellular matrix (ECM) components, especially collagen, within the lung tissue. This remodeling of the alveolar architecture disrupts normal gas exchange and significantly compromises respiratory function, ultimately leading to respiratory failure and death in severe cases (Wynn and Ramalingam, 2012; Barratt *et al.*, 2018). As the global population ages, the incidence of age-associated pulmonary fibrosis is expected to rise, further compounding the public health burden (Kumar et al., 2024). Idiopathic pulmonary fibrosis (IPF), a form of pulmonary fibrosis, occurs primarily in older adults, often with characteristic imaging and histologic appearances (Lederer and Martinez, 2018). The disease is typically diagnosed late, leading to high mortality rates, as there is currently no cure and limited therapeutic options available.

Aging is intrinsically linked with a decline in regenerative capacity and increased oxidative stress, which accelerates degenerative changes in pulmonary tissue (Wang et al., 2021). Cellular senescence, mitochondrial dysfunction, chronic inflammation, and telomere attrition have all been implicated in the onset and progression of pulmonary fibrosis in elderly individuals (López-Otín *et al.*, 2013; Guzonjić *et al.*, 2022; Zeng *et al.*, 2024). Notably, reactive oxygen species (ROS) and lipid peroxidation products such as malondialdehyde (MDA) have emerged as key contributors to epithelial injury and fibrogenesis (Cheresh *et al.*, 2013; Ayala, Muñoz and Argüelles, 2014). Oxidative stress has been further implicated as a major driver of IPF, exacerbating the disease through the production of ROS and pro-inflammatory cytokines that promote epithelial injury and fibrosis (Cameli *et al.*, 2020).

Cigarette smoke exposure worsens this process by continuously producing ROS and pro-inflammatory cytokines, which cause persistent oxidative stress, epithelial cell apoptosis, and collagen deposition (Kim, Suh and Mun, 2004; Yao et al., 2008; Coleman-Belin et al., 2023). The central role of oxidative damage in driving pulmonary fibrosis highlights the therapeutic potential of antioxidants in slowing disease progression (Sharma & Wairkar, 2024). Idiopathic pulmonary fibrosis (IPF) patients often show an imbalance between oxidants and antioxidants, contributing to disease progression and worsening fibrosis (Cameli *et al.*, 2020). Therefore, targeting this oxidative imbalance with natural antioxidants could offer a promising approach for treatment.

Recently, there has been increasing interest in Lycium barbarum, commonly known as Goji berry, due to its powerful antioxidant, anti-inflammatory, and immunomodulatory properties (Li & Kan, 2017). Rich in polysaccharides (LBP), flavonoids, carotenoids, and phenolic compounds, Goji berry exhibits biological activities that target multiple pathogenic pathways in lung fibrosis, including ROS neutralization, inhibition of NF-κB signaling, and attenuation of collagen deposition (Niu *et al.*, 2008; Ma *et al.*, 2019). As oxidative stress plays a central role in IPF progression, Goji berry's potential to reduce ROS levels and inflammation may provide an effective adjunct to conventional therapies for IPF, as demonstrated in preclinical studies (Lederer and Martinez, 2018).

This review examines the interconnected roles of collagen accumulation, pulmonary fibrosis, and aging, and highlights the potential of Goji berry as a natural intervention for reducing fibrotic lung damage. Understanding the molecular interactions between oxidative stress, aging, and fibrogenesis could lead to new strategies in anti-aging and pulmonary medicine. Through better understanding of oxidative stress and its management, we could envision better therapeutic outcomes for diseases like idiopathic pulmonary fibrosis (IPF) (Lederer and Martinez, 2018; Cameli *et al.*, 2020).

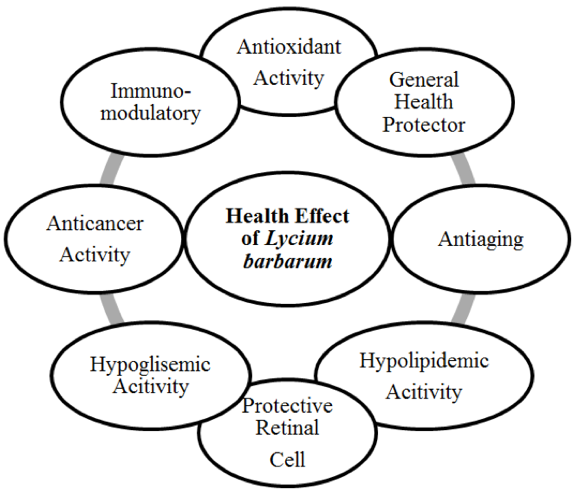
The beneficial effects of *Lycium barbarum*, which include antioxidant, anti-aging, anticancer, and anti-inflammatory properties, are visually summarized in Figure 1.

Fig. 1. Health Effects of *Lycium barbarum* (Kocyigit and Sanlier, 2017)

2. PATHOGENESIS OF PULMONARY FIBROSIS

Pulmonary fibrosis (PF) is a progressive lung disorder characterized by excessive collagen accumulation in the lung parenchyma, leading to disrupted gas exchange and impaired respiratory function. This process is driven by a combination of oxidative stress, inflammation, and collagen accumulation. As the global population ages, the incidence of PF, particularly IPF, increases, with aging contributing to a decline in lung regenerative capacity and an imbalance in the redox state of the lung tissue (Lederer and Martinez, 2018).

Oxidative stress plays a central role in the development of PF. Reactive oxygen species (ROS), generated by both endogenous metabolic processes and external factors such as smoking or pollution, activate signaling pathways that promote fibrogenesis. TGF-β (Transforming Growth Factor-Beta), a critical mediator in fibrosis, stimulates fibroblasts to produce excessive collagen and ECM components. ROS also contribute to the activation of NF-kB, a transcription factor that drives the expression of pro-inflammatory cytokines like TNF-α and IL-6, further exacerbating fibrosis by promoting fibroblast activation and collagen deposition (Wynn and Ramalingam, 2012; Cheresh et al., 2013).

In addition to oxidative stress, inflammation plays a pivotal role in the progression of fibrosis. Initially, lung injury triggers an inflammatory response where epithelial cells and macrophages release cytokines and chemokines, recruiting immune cells that contribute to tissue damage. Chronic inflammation leads to the continuous activation of fibroblasts, myofibroblasts, and fibrocytes (bone marrow-derived cells), which secrete collagen and further remodel the ECM (Koli et al., 2008; Barnes, 2014). This persistent inflammatory response, coupled with the activation of pro-fibrotic signaling pathways, impedes normal tissue repair and accelerates the progression of fibrosis (Wynn and Ramalingam, 2012).

3. goji berry and its constituents

Goji berry (*Lycium barbarum*) is a nutrient-rich fruit known for its potential health benefits, particularly due to its high content of bioactive compounds. These compounds, such LBP, flavonoids, carotenoids, and phenolic compounds, contribute significantly to the berry's antioxidant, anti-inflammatory, and immunomodulatory effects. Traditionally used in chinese medicine, Goji berry has recently gained global attention due to its reported benefits in enhancing immune function, longevity, and overall health (Kocyigit and Sanlier, 2017).

The primary active compounds in Goji berry are LBP, which are the most studied components. LBP have been shown to scavenge ROS, which play a key role in the pathogenesis of various diseases, including pulmonary fibrosis. This reduction in ROS helps mitigate oxidative stress, a major contributor to the development of fibrosis. Additionally, flavonoids and carotenoids, particularly zeaxanthin and beta-carotene, contribute to the antioxidant capacity of Goji berry, further protecting cells from oxidative damage and supporting lung health (Li, Ma and Liu, 2007; Ma et al., 2019).

4. mechanistic pathways in collagen modulation

While Goji berry (*Lycium barbarum*) is rich in bioactive compounds, its direct impact on collagen modulation and fibrotic remodeling in pulmonary fibrosis is a key focus of its therapeutic potential. Unlike its more general role as an antioxidant and anti-inflammatory agent (discussed in Section 3), Goji berry’s specific mechanisms of action in collagen modulation highlight its potential in fibrosis treatment. These mechanisms include antioxidant enhancement, fibrogenic signaling regulation, and collagen synthesis inhibition.

A major mechanism by which Goji berry helps modulate collagen deposition in pulmonary fibrosis is through its antioxidant activity. LBP significantly reduce ROS, which are elevated in fibrotic lungs and contribute to the activation of fibrogenic pathways. LBP enhance the activity of key antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), thereby reducing oxidative stress that otherwise exacerbates fibrosis. By decreasing ROS, Goji berry helps to protect lung cells and prevent excessive collagen deposition(Li, Ma and Liu, 2007).

Goji berry also exerts its therapeutic effects by directly regulating the fibrogenic pathways responsible for collagen synthesis. It does so by inhibiting TGF-β, a key regulator of fibrosis that stimulates the production of collagen by fibroblasts and myofibroblasts. TGF-β is one of the most potent fibrogenic factors in pulmonary fibrosis, and its inhibition by Goji berry can help balance collagen synthesis and degradation (Niu et al., 2008; Ma et al., 2019). Furthermore, Goji berry modulates the activity of matrix metalloproteinases (MMPs), enzymes responsible for degrading the ECM, helping to maintain a balanced matrix remodeling process and preventing excessive fibrosis (Ma et al., 2019).

In addition to these mechanisms, goji berry also inhibits NF-kB, a critical transcription factor that drives the expression of pro-inflammatory cytokines. This inhibition reduces inflammation in the lungs, further mitigating the fibrotic response. By reducing inflammation and oxidative stress while regulating collagen deposition, goji berry plays a multifaceted role in attenuating fibrosis (Cheresh et al., 2013; Ma et al., 2019).

5. Current Therapies for Pulmonary Fibrosis and Comparison with Goji Berry

Pulmonary fibrosis is commonly treated using pharmacological agents like pirfenidone and nintedanib, which aim to slow disease progression by targeting key pathways in fibrosis, such as TGF-β signaling and fibroblast activation. While these treatments have been shown to reduce the rate of lung function decline, they come with a range of side effects, including gastrointestinal discomfort, liver toxicity, and fatigue (Lederer and Martinez, 2018). Furthermore, these therapies do not address the underlying oxidative stress or inflammation that contribute to fibrotic remodeling in the lungs.

Table 1. Goji berry vs. conventional therapies for pulmonary fibrosis (Lederer and Martinez, 2018)

| **Therapy/Agent** | **Mechanism of Action** | **Efficacy** | **Side Effects** |
| --- | --- | --- | --- |
| Pirfenidone | Inhibits TGF-β, reduces fibroblast activity | Slows lung function decline | Gastrointestinal discomfort, fatigue, liver toxicity |
| Nintedanib | Inhibits VEGF, FGF, and PDGF signaling | Reduces decline in lung function | Diarrhea, liver dysfunction, risk of bleeding |
| Goji Berry (*Lycium barbarum*) | Antioxidant, anti-inflammatory, modulates collagen synthesis | Reduces oxidative damage, modulates inflammation, prevents excessive fibrosis | Generally safe, minimal side effects reported |

In contrast, Goji berry (*Lycium barbarum*) offers a more natural approach with its antioxidant, anti-inflammatory, and immunomodulatory properties, making it a promising adjunctive treatment for pulmonary fibrosis. Studies have shown that LBP, the primary active components of Goji berry, have significant antioxidant activity, measured by their ORAC (Oxygen Radical Absorbance Capacity) value, which indicates their ability to neutralize free radicals. According to Zhang (2013), Goji berry has a high ORAC score, highlighting its potent antioxidant capacity, which is crucial for protecting lung tissue from oxidative damage in diseases like pulmonary fibrosis (Zhang, 2013).

Table 2. ORAC Score difference between Goji berry and other fruits (Zhang, 2013)

| **Fruit Name** | **ORAC Score (µmol TE/gr dry weight)** |
| --- | --- |
| *Goji berry* | 188,52±1,3 |
| Strawberry | 153,6±7,5 |
| Plum | 79,1±1,9 |
| Orange | 51,7±2,7 |
| Red grape | 36,0±1,1 |
| Kiwi | 36,5±1,3 |
| Banana | 9,0±0,4 |
| Apple | 13,2±0,9 |
| Tomato | 37,8±0,5 |
| Pear | 9,6±0,2 |
| Melon | 12,9±0,5 |

In addition to antioxidant activity, Goji berry modulates inflammatory pathways by inhibiting NF-κB signaling, thus reducing the production of pro-inflammatory cytokines like TNF-α and IL-6, which are involved in fibrosis. This contrasts with conventional therapies, which primarily focus on collagen deposition and fibroblast activation, but do not directly target the oxidative stress and inflammation that drive fibrosis (Wynn and Ramalingam, 2012; Cheresh et al., 2013).

6. METHODS

This article is presented as a narrative literature review, aiming to synthesize existing scientific evidence and theoretical perspectives from previously published research articles. Relevant studies were gathered through systematic searches across several scholarly databases including Google Scholar, PubMed, ScienceDirect, and SpringerLink.

The literature search used a combination of keywords such as: “Goji Berry”, “Lycium barbarum”, “Pulmonary Fibrosis”, “Collagen”, “Oxidative Stress”, and “Aging Lung”. The selection focused on articles published within 2004 and 2024 to ensure relevance to current scientific developments.

Inclusion criteria for selected sources were: (1) peer-reviewed journal articles; (2) studies published in English; and (3) publications investigating the role of *Lycium barbarum* or its extracts in relation to oxidative stress, aging-related tissue degeneration, or pulmonary fibrosis. Articles that were inaccessible in full text, non-peer-reviewed conference proceedings, and case reports or case series were excluded.

Eligible articles were reviewed and analyzed for critical information regarding experimental models, biological mechanisms, outcome measures, and therapeutic implications. Emphasis was placed on extracting data related to antioxidant activity, modulation of collagen deposition, and the attenuation of fibrotic markers. The findings were synthesized thematically to provide a comprehensive overview of the potential of *Lycium barbarum* in mitigating collagen-associated pulmonary damage.

7. results and discussion

The initial literature curation, based on the specified keywords, yielded a total of 15 cited studies related to aging, oxidative stress, collagen remodeling, and *Lycium barbarum* (Goji berry). After screening for topic relevance and experimental focus, particularly regarding pulmonary fibrosis and antioxidant interventions, three (3) full-text articles were selected for final inclusion. These studies directly examined the protective effects of Goji berry extract or its bioactive polysaccharides (LBP) on lung oxidative injury, inflammation, and fibrotic remodeling.

The selected articles are summarized in Table 3, which outlines the experimental models, type of Goji berry intervention, key biological outcomes, and resulting conclusions.

**Table 3. Research investigates the effects of Goji berry extract on pulmonary fibrosis**

| **Author** | **Sample** | **Intervention** | **Result** | **Conclusion** |
| --- | --- | --- | --- | --- |
| Li, Ma and Liu (2007) | Male Kunming mice (20–22 months old), n=10 per group, divided into 4 groups: control and LBP-treated (200, 300, 400 mg/kg). Treatment duration: 20 days via oral gavage. | LBP was administered orally at doses of 200, 300, and 400 mg/kg/day for 20 consecutive days. Lung tissue was harvested for analysis of SOD, CAT, GSH-Px activities, and MDA and lipofuscin content as oxidative stress markers. | At 400 mg/kg LBP, SOD, CAT, and GSH-Px activities in lung tissue increased by 31.8%, 39.6%, and 44.5% respectively compared to control. MDA reduced by 27.3%, and lipofuscin content decreased significantly (p<0.05). | LBP at 400 mg/kg/day demonstrated strong antioxidant capacity in aged lungs, restoring enzymatic defenses and reducing peroxidative damage, suggesting potential for fibrosis prevention in age-related pulmonary degeneration. |
| Niu et al. (2008) | Male Wistar rats, n=10 per group, divided into 5 groups: sedentary control, exercise control, and LBP-treated (100, 200, 300 mg/kg/day) groups. Treadmill training: progressive overload to exhaustion for 30 days. | LBP was given orally at doses of 100, 200, and 300 mg/kg/day for 30 days. Treadmill regimen included 5 days/week exercise with progressive intensity. Antioxidant status measured via serum and muscle SOD, GPx, and MDA assays. | 300 mg/kg/day LBP increased SOD by 41.2% and GPx by 35.6%, while MDA and CK levels decreased by 29.8% and 22.7% compared to exercise-only group. Improvements were dose-dependent and statistically significant (p<0.01). | Systemic LBP administration at 300 mg/kg/day effectively mitigated exercise-induced oxidative stress, with implications for reducing risk of oxidative lung damage in high-stress physiological conditions. |
| Ma et al. (2019) | Male Wistar rats, n=10 per group, exposed to 12 unfiltered cigarettes/day (2×/day for 28 days). LBP treatment groups received 100 or 200 mg/kg/day orally during the same period. | Rats were exposed to cigarette smoke in a 27×18×14 cm chamber. LBP was administered orally at 100 mg/kg and 200 mg/kg/day. Lung samples analyzed for TNF-α, IL-6, IL-8 (via ELISA), MDA (via TBA method), SOD, GSH-Px, and histology. NF-κB expression assessed via immunohistochemistry. | 200 mg/kg/day LBP decreased TNF-α, IL-6, and IL-8 by 37.9%, 34.2%, and 31.6% respectively; MDA reduced by 42.8%, while SOD and GSH-Px increased by 45.7% and 40.3%. Lung histology showed reduced alveolar thickening and inflammatory infiltration. NF-κB expression downregulated significantly. | LBP at 200 mg/kg/day significantly suppressed inflammatory cytokines and oxidative damage in cigarette smoke-induced lung injury, confirming its therapeutic relevance in preventing or treating pulmonary fibrosis via NF-κB inhibition. |

As the human body undergoes the natural process of aging, significant structural and functional changes take place in the lungs. These changes include diminished pulmonary elasticity, thinning of alveolar walls, and a decline in the antioxidant defense system, which makes the lungs more susceptible to oxidative stress and chronic inflammation. One of the most concerning consequences is the excessive accumulation of extracellular matrix proteins, particularly collagen, which plays a central role in the development of pulmonary fibrosis. This condition is marked by irreversible scarring of the lung tissue and is commonly associated with aging, exposure to environmental toxins such as cigarette smoke, and the accumulation of reactive oxygen species (ROS) (Li, Ma and Liu, 2007; Ma *et al.*, 2019).

The imbalance between ROS generation and the antioxidant defense system in aging lungs leads to cellular damage, inflammatory signaling, and ultimately, fibrotic remodeling. ROS can activate nuclear factor-kappa B (NF-κB), a key transcription factor that promotes the release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-8, all of which further stimulate fibroblast proliferation and collagen deposition (Ma *et al.*, 2019). In this context, enhancing the antioxidant capacity of lung tissue becomes a rational therapeutic strategy for preventing or attenuating fibrotic damage.

Among various natural antioxidant sources, Goji berry (Lycium barbarum) has attracted considerable attention due to its rich content of Lycium barbarum polysaccharides (LBP), carotenoids, flavonoids, and phenolic acids (Donno *et al.*, 2015; Kulczyński and Gramza-Michałowska, 2016). LBP is the most abundant and bioactive compound in Goji berry, making up approximately 5–8% of the fruit’s dry weight, and is known to enhance enzymatic antioxidant defenses, reduce lipid peroxidation, and modulate inflammation.

Li, Ma and Liu (2007) conducted one of the earliest studies examining the effects of LBP in aged mice, administering oral doses of 200, 300, and 400 mg/kg/day for 20 consecutive days. Their results demonstrated that LBP significantly elevated the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in lung tissue while simultaneously reducing levels of malondialdehyde (MDA) and lipofuscin, key markers of oxidative damage. At the highest dose of 400 mg/kg, SOD activity increased by 31.8%, CAT by 39.6%, and GSH-Px by 44.5%, while MDA levels were reduced by 27.3%. These findings suggest that LBP is effective in restoring redox balance and protecting lung tissue from age-related oxidative injury.

While not focused specifically on pulmonary tissue, the study by (Niu *et al.*, 2008) explored systemic oxidative stress in Wistar rats subjected to exhaustive treadmill exercise and found that LBP supplementation at 100–300 mg/kg/day for 30 days significantly improved antioxidant status. In the 300 mg/kg group, SOD activity rose by 41.2%, and GPx by 35.6%, while MDA levels decreased by nearly 30%. These improvements imply a broad systemic antioxidant effect of LBP that may extend to lung tissues, especially under conditions of physiological stress.

More recently, Ma et al. (2019) provided direct evidence of LBP’s protective role in pulmonary fibrosis by using a cigarette smoke-induced lung injury model in rats. Over a 28-day period, LBP at doses of 100 and 200 mg/kg/day was administered concurrently with cigarette smoke exposure. The treatment led to significant reductions in TNF-α (−37.9%), IL-6 (−34.2%), and IL-8 (−31.6%) concentrations in lung tissue, alongside a 42.8% decrease in MDA levels. Additionally, SOD and GSH-Px levels increased by 45.7% and 40.3% respectively. Histopathological analysis revealed diminished inflammatory cell infiltration and alveolar wall thickening, while immunohistochemical studies confirmed the downregulation of NF-κB expression in lung tissues.

The consistency of these findings across diverse experimental models strengthens the conclusion that LBP plays a multifactorial protective role in the lungs. It restores antioxidant capacity, inhibits inflammatory signaling, and reduces fibrotic remodeling, all of which are critical in preventing the progression of pulmonary fibrosis. Although further studies, especially in human populations, are required to confirm these effects, the preclinical evidence presents a compelling case for considering Goji berry as a natural therapeutic agent against oxidative lung injury and age-related fibrosis.

8. Conclusion

Pulmonary fibrosis is closely linked to aging and oxidative stress, which impair lung structure through excessive collagen accumulation and chronic inflammation. The decline in endogenous antioxidants with age contributes to redox imbalance and activation of fibrotic pathways.

Goji berry (*Lycium barbarum*), particularly through its Lycium barbarum polysaccharides (LBP), has shown consistent protective effects in preclinical models. LBP enhances antioxidant enzyme activity, reduces oxidative damage, suppresses inflammatory cytokines, and inhibits NF-κB signaling. These mechanisms collectively attenuate lung tissue damage and fibrotic remodeling.

Findings from aging and smoke-induced lung injury models support the potential of Goji berry as a natural therapeutic agent against pulmonary fibrosis. While further human studies are needed, current evidence highlights its promise in reducing age-related and environmentally driven lung damage through antioxidant and anti-inflammatory action.

However, despite these promising preclinical findings, clinical evidence is still limited, and standardized dosage regimens for Goji berry are yet to be established. Additionally, large-scale human clinical trials are necessary to confirm its efficacy and fully understand the long-term therapeutic benefits and safety profile in patients with pulmonary fibrosis. The combination of Goji berry with current therapies and its possible synergistic effects also warrants further exploration to optimize its potential in clinical practice.

disclaimer (Artificial intelligence)

The author(s) confirm that generative AI tools, including Large Language Models, were used in the process of writing or editing this manuscript.

**Details of AI usage:**

AI assistance was used only in approximately 2 to 3 instances. The tool utilized was ChatGPT, accessed via chatgpt.com. It was used specifically to paraphrase certain sentences in order to avoid direct plagiarism from the referenced journal texts.

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