Mulberry Leaf (Morus alba) in Respiratory Health

From Bioactive Constituents and Mechanistic Pathways to Nutritional Intervention Strategies

Abstract

Background: Respiratory diseases share common pathological drivers - including chronic inflammation, oxidative stress, and metabolic dysregulation - that amplify airway injury, alveolar remodeling, and cardiopulmonary burden.

Patients with comorbid diabetes or metabolic syndrome often experience more severe outcomes due to postprandial hyperglycemia and insulin surges, which intensify systemic inflammatory and oxidative responses.

Objective: To evaluate mulberry leaf (*Morus alba*) as a nutritional pharmacological intervention for respiratory diseases, integrating its phytochemical basis, mechanistic pathways, and clinical evidence.

Bioactive Constituents: Mulberry leaf contains multiple bioactive compounds, including 1-deoxynojirimycin (DNJ, a natural α-glucosidase inhibitor), flavonoids (quercetin derivatives, rutin, and isoquercitrin), polyphenols (chlorogenic acid), polysaccharides, and phytosterols.

Mechanistic Pathways:

Author: Xu Jin & Keyora | ORCID: 0009-0007-5798-1996

1) Metabolic regulation: DNJ-mediated inhibition of α-glucosidase reduces postprandial glucose and insulin excursions, attenuating advanced glycation end-product (AGE) formation and limiting metabolic stress–induced activation of NF-κB.
2) Anti-inflammatory activity: Flavonoids and polyphenols suppress NF-κB and MAPK signaling, downregulating pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and reducing systemic inflammatory burden.
3) Antioxidant defense: Chlorogenic acid and polysaccharides enhance endogenous antioxidant enzymes (SOD, CAT, GSH-Px), lower malondialdehyde (MDA) levels, and mitigate oxidative epithelial and alveolar damage.
4) Immunomodulation: Polysaccharides restore Th1/Th2 balance, reduce mast cell–mediated allergic responses, and enhance antiviral defense.
5) Vascular and cardiopulmonary protection: Phytosterols improve lipid profiles (LDL-C reduction, HDL-C elevation) and endothelial function, lowering pulmonary circulatory pressure and supporting cardiopulmonary coupling.

Clinical Evidence: Randomized controlled trials in pre-diabetic, type 2 diabetes, and metabolic syndrome populations consistently show improvements in HbA1c, fasting glucose, lipid profiles, and inflammatory markers (CRP, IL-6, TNF-α), accompanied by increased antioxidant capacity. Longer-term interventions demonstrate vascular benefits, including reduced carotid intima–media thickness and improved endothelial function, which have translational relevance for chronic obstructive pulmonary disease (COPD), asthma, and pulmonary fibrosis.

Conclusion: Mulberry leaf functions as a systemic “background modulator” of inflammation-oxidative stress-metabolic coupling. Its integration into respiratory disease management, particularly in patients with metabolic comorbidities, may reduce acute exacerbation triggers, stabilize chronic inflammatory baselines, and enhance cardiopulmonary outcomes.

When combined with complementary nutrients (elderberry, quercetin, vitamin C, zinc, bromelain), mulberry leaf contributes to a multidimensional nutritional intervention framework for respiratory health.

Keywords

Morus alba; 1-Deoxynojirimycin; α-Glucosidase Inhibitors; Postprandial Hyperglycemia; Advanced Glycation End Products; NF-κB Signaling; MAPK Pathway; Pro-inflammatory Cytokines (IL-6, TNF-α, IL-1β); Oxidative Stress; Reactive Oxygen Species; Antioxidant Enzymes (SOD, Catalase, Glutathione Peroxidase); Malondialdehyde; Th1/Th2 Balance; Mast Cells; Allergic Respiratory Diseases; Chronic Obstructive Pulmonary Disease; Asthma; Pulmonary Fibrosis; Endothelial Function; Cardiopulmonary Circulation; Nutritional Pharmacology

The progression of respiratory diseases is profoundly influenced by metabolic status. Acute hyperglycemia and insulin surges can impair immune function and increase susceptibility to infection. In chronic respiratory disorders such as chronic obstructive

pulmonary disease (COPD) and asthma, patients with comorbid diabetes or metabolic syndrome exhibit more severe inflammatory responses and poorer clinical outcomes. Thus, the regulation of postprandial glucose and insulin peaks is not only a therapeutic target in diabetes but also a critical strategy at the intersection of respiratory and metabolic health.

Mulberry leaf (*Morus alba*), a member of the Moraceae family, has long been consumed across East Asia, South Asia, South America, and the Mediterranean for both dietary and health purposes. Modern nutritional science and clinical research have demonstrated that mulberry leaves are rich in diverse bioactive constituents, including alkaloids (notably 1-deoxynojirimycin, DNJ), flavonoids (quercetin, rutin, isoquercitrin), polyphenols (chlorogenic acid), polysaccharides, and phytosterols.

These compounds provide the molecular foundation for its multifaceted physiological effects, encompassing metabolic regulation, control of inflammation and oxidative stress, and vascular and circulatory protection.

Multiple human clinical trials have confirmed that supplementation with mulberry leaf preparations significantly reduces postprandial glucose and insulin responses, while improving lipid profiles and inflammatory markers.

Collectively, these findings have facilitated the transition of mulberry leaf from a “traditional herbal agent” to an “evidence-supported nutritional intervention factor,” thereby establishing a novel theoretical and practical foundation for its application in the nutritional management of respiratory diseases.

Author: Xu Jin & Keyora | ORCID: 0009-0007-5798-1996

I Bioactive Constituents of Mulberry Leaf and Their Core Functional Basis

Nutritional Pharmacological Foundations of Multidimensional Bioactive Compounds in the Regulation of Inflammation and Oxidative Stress

Modern studies have progressively elucidated the rich phytochemical spectrum of mulberry leaf (*Morus alba*), encompassing alkaloids (with 1-deoxynojirimycin, DNJ, as the representative), flavonoids (such as quercetin derivatives and rutin), polyphenols (predominantly chlorogenic acid), polysaccharides, and phytosterols. These multidimensional bioactive compounds not only confer unique value to mulberry leaf in glucose, lipid, and metabolic regulation but also constitute its fundamental basis for modulating inflammation and oxidative stress.

Inflammatory responses and oxidative stress are central pathological mechanisms underlying the onset and progression of respiratory diseases, including chronic obstructive pulmonary disease (COPD), asthma, acute respiratory distress syndrome (ARDS), and pulmonary fibrosis. Excessive release of inflammatory cytokines and the accumulation of reactive oxygen species (ROS) result in airway injury, alveolar structural damage, and dysregulation of immune homeostasis. Bioactive constituents of mulberry leaf exert potential nutritional pharmacological benefits by activating antioxidant signaling pathways, downregulating pro-inflammatory mediators, and restoring immune balance.

Therefore, an in-depth mechanistic analysis of mulberry leaf, based on its nutritional pharmacological characteristics and anchored in the central axis of “inflammation–

oxidative stress," is essential for advancing its transition from a traditional herbal remedy to an evidence-supported nutritional intervention factor.

1) Alkaloids: 1-Deoxynojirimycin (DNJ)

1-Deoxynojirimycin (DNJ) is the most representative alkaloid in mulberry leaf and is a naturally occurring α-glucosidase inhibitor. Clinical studies have demonstrated that DNJ significantly reduces postprandial glucose peaks and insulin levels.

- **Respiratory Implications of Postprandial Hyperglycemia and Systemic Inflammation**

Abrupt elevations in postprandial glucose and insulin are not only hallmarks of metabolic dysregulation but also potent triggers of systemic inflammation and oxidative stress. Excessive glucose load promotes the formation of advanced glycation end-products (AGEs) and activates redox-sensitive transcription factors such as NF-κB, thereby increasing the release of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).

This amplified inflammatory response exacerbates airway inflammation during acute respiratory infections (e.g., influenza or coronavirus infection) and accelerates airway remodeling and alveolar destruction in chronic obstructive pulmonary disease (COPD), ultimately worsening respiratory function.

- **Systemic Improvement of Metabolic Inflammation by 1-Deoxynojirimycin (DNJ) Intervention**

Multiple human clinical trials have confirmed that mulberry leaf preparations can effectively improve glucose metabolism and reduce inflammatory burden. In populations with prediabetes and type II diabetes, supplementation with mulberry leaf extract significantly decreases HbA1c and fasting blood glucose levels, while concomitantly lowering inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). Alleviation of systemic inflammation is of direct relevance to patients with respiratory diseases: reducing chronic inflammatory activity not only restores metabolic homeostasis but also mitigates sustained injury to the airways and alveoli, thereby providing protective support for respiratory function.

- **Respiratory Benefits in Patients with Metabolic Comorbidities**

In patients with chronic obstructive pulmonary disease (COPD) complicated by metabolic syndrome or diabetes, inflammation and metabolic dysregulation often form a “vicious cycle”: hyperglycemia and insulin resistance exacerbate inflammation, while persistent inflammation further impairs pancreatic function and tissue repair. DNJ in mulberry leaf, by inhibiting α-glucosidase and delaying carbohydrate absorption, effectively controls postprandial glycemic responses while exerting anti-inflammatory effects.
This dual mechanism not only improves metabolic indices but also reduces the inflammatory load within the pulmonary environment, thereby enhancing overall disease management in COPD patients. Such effects are particularly valuable in subgroups with concurrent metabolic disorders, highlighting DNJ’s potential clinical significance.

2) Anti-Inflammatory and Antioxidant Roles of Mulberry Leaf Flavonoids in Respiratory Disease Intervention

Flavonoid nutrients possess strong anti-inflammatory and antioxidant potential. They can suppress the NF-κB signaling pathway, thereby reducing inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), while simultaneously enhancing antioxidant capacity. Human studies consistently demonstrate that flavonoid supplementation is associated with reductions in inflammatory markers and improvements in antioxidant defense.

- **Core Inflammatory Mechanisms in Asthma and COPD**

Asthma and chronic obstructive pulmonary disease (COPD) are both characterized by chronic airway inflammation and oxidative stress. Airway infiltration by inflammatory cells (eosinophils, neutrophils, macrophages), along with elevated levels of cytokines (IL-4, IL-5, IL-13, TNF-α), leads to airway hyper-responsiveness and structural remodeling. At the same time, excessive accumulation of reactive oxygen species (ROS) exacerbates epithelial injury and amplifies inflammatory cascades. Flavonoid compounds in mulberry leaf - such as quercetin derivatives, rutin, and isoquercitrin - can inhibit the NF-κB signaling pathway and MAPK cascades, thereby suppressing cytokine expression and reducing free radical generation. These effects establish a biological foundation for improving the airway inflammatory milieu and alleviating hyper-responsive states.

- **Epithelial Protection in Acute Respiratory Infections**

During acute respiratory infections (e.g., influenza or coronavirus infection), virus-induced hyper-inflammation often disrupts the airway epithelial barrier and impairs ciliary function, prolonging recovery. Mulberry leaf flavonoids mitigate these effects through enhanced antioxidant defenses (elevating glutathione levels and scavenging ROS) and downregulation of pro-inflammatory cytokines. These actions help protect airway epithelium, improve local inflammatory conditions, reduce disease severity, and potentially shorten recovery time, thereby strengthening host respiratory defenses.

- **Immunoregulatory Potential in Allergic Respiratory Diseases**

In allergic respiratory diseases such as allergic rhinitis and asthma, mast cell activation and the release of inflammatory mediators (histamine, leukotrienes, prostaglandins) play central roles in symptom manifestation. Studies suggest that flavonoids inhibit mast cell degranulation, decrease mediator release, and suppress IgE-mediated allergic responses. Through these mechanisms, mulberry leaf flavonoids may improve clinical symptoms in allergic respiratory disease patients, including nasal congestion, cough, and airway spasms.

3) The Role of Mulberry Leaf Polyphenols-Chlorogenic Acid-in Respiratory Disease Intervention

Multiple human clinical studies have demonstrated that chlorogenic acid, a polyphenolic compound found in mulberry leaves, exerts significant effects on glycemic regulation, lipid improvement, and anti-inflammatory as well as antioxidant defense.

Mechanistically, chlorogenic acid enhances the activity of endogenous antioxidant enzymes - including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) - while reducing the formation of lipid peroxidation products such as malondialdehyde (MDA). These actions collectively attenuate oxidative damage to cellular membranes and tissue structures.

Beyond improving metabolic homeostasis, chlorogenic acid provides a solid biochemical foundation for protecting the body against chronic inflammatory environments.

- **Antioxidant Protection in Chronic Respiratory Diseases**

In chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma, and pulmonary fibrosis, oxidative stress is a critical driver of airway structural injury and progressive loss of lung function. Persistent inflammatory stimulation promotes excessive free radical production, leading to epithelial cell damage and alveolar destruction. By enhancing antioxidant defense systems and reducing MDA levels, chlorogenic acid effectively mitigates free radical-induced cellular injury, thereby slowing pathological progression in chronic respiratory conditions.

This protective effect plays an important role in alleviating airway inflammatory environments and preserving pulmonary function.

- **Respiratory Protection in High-Risk Populations**

Individuals exposed to cigarette smoke, occupational dust, or environmental pollutants are often subjected to heightened inflammatory and oxidative stress burdens, rendering

airway epithelial cells and alveolar structures particularly vulnerable. Chlorogenic acid's antioxidant activity not only reduces oxidative stress but may also attenuate inflammatory mediator release, thereby maintaining airway barrier integrity.

At the population level, its application provides additional nutritional protection against adverse respiratory health outcomes associated with environmental and lifestyle-related risk factors.

4) Immunomodulatory and Respiratory Protective Roles of Mulberry Leaf Polysaccharides

Mulberry leaf polysaccharides have been shown in multiple human and cellular studies to improve inflammatory markers and enhance antioxidant capacity. Their primary mechanisms are closely related to the regulation of immune responses. Specifically, they help rebalance T helper cell subsets (Th1/Th2), thereby preventing skewed immune responses that lead to inflammatory dysregulation.

In parallel, polysaccharides promote the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reducing the levels of free radicals and lipid peroxidation products, and providing the body with comprehensive anti-inflammatory and antioxidant support.

- **Defensive Support in Acute Respiratory Infections**

In populations affected by acute respiratory infections, impaired immune function is a major reason for more severe symptoms and prolonged disease course. Infection is often

accompanied by cytokine storms and heightened oxidative stress, which compromise the airway epithelial barrier.

The immunomodulatory effects of mulberry leaf polysaccharides enhance Th1 cell–mediated antiviral responses while simultaneously reducing excessive cytokine release, thereby restoring balance between immune defense and inflammatory control. Additionally, their antioxidant effects help minimize infection-related oxidative damage, thus accelerating recovery.

- **Immune Balancing Effects in Allergic Respiratory Diseases**

In conditions such as asthma and allergic rhinitis, overactive Th2 cell responses represent a key pathological mechanism driving allergic inflammation. Excessive activation of the Th2 pathway elevates cytokines including IL-4, IL-5, and IL-13, thereby inducing airway hyper-responsiveness and worsening inflammation. Mulberry leaf polysaccharides counteract this by suppressing Th2 hyperactivity and promoting moderate Th1 activation, effectively restoring immune homeostasis.

Such actions help reduce allergic inflammation, stabilize airway function, and relieve the clinical burden in patients with asthma and other allergic respiratory conditions.

5) Phytosterols

Phytosterols are natural compounds structurally similar to cholesterol, capable of lowering plasma cholesterol levels by competitively inhibiting cholesterol absorption in the small intestine. Clinical studies in humans have shown that mulberry leaf

preparations significantly reduce low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), while increasing high-density lipoprotein cholesterol (HDL-C).
This lipid-modulating effect not only improves overall lipid profiles but also lowers the risk of atherosclerosis and cardiovascular disease, thereby providing systemic health benefits to patients with respiratory disorders.
In addition, phytosterols have been shown to exhibit anti-inflammatory and antioxidant properties, further reducing vascular and tissue inflammatory burden.

- **Pulmonary Circulatory Protection in Chronic Respiratory Diseases**

In chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, patients often experience increased pulmonary circulatory burden and impaired endothelial function.
Chronic inflammation and hypoxia can lead to pulmonary hypertension, increased right ventricular load, and disruption of cardiopulmonary coupling.
By improving lipid metabolism and vascular endothelial function, phytosterols help alleviate pulmonary circulatory pressure, maintain vascular elasticity and permeability, and enhance cardiopulmonary interactions.
These effects hold potential value in delaying disease progression, improving exercise tolerance, and enhancing quality of life.

- **Systemic Benefits in Patients with Cardiovascular Risk**

Patients with respiratory diseases - particularly those with COPD or interstitial lung disease - frequently present with elevated cardiovascular risk factors, including coronary

artery disease, hypertension, and metabolic syndrome. In this population, the circulatory protective role of phytosterols is especially relevant.

By lowering LDL-C, increasing HDL-C, and reducing inflammation and oxidative damage, phytosterols can mitigate the risk of cardiovascular complications, thereby improving overall prognosis.

Thus, mulberry leaf phytosterols serve not only as regulators of metabolic health but also as essential nutritional support for integrated cardiopulmonary protection in respiratory patients.

6) Summary

Clinical evidence has demonstrated that the bioactive constituents of mulberry leaf exert three major functions: metabolic regulation, anti-inflammatory and antioxidant defense, and circulatory protection.

These mechanisms hold direct translational value for respiratory diseases:

- Metabolic regulation → mitigates hyperglycemia-induced inflammation and oxidative stress, thereby improving the systemic inflammatory background in respiratory disorders
- Anti-inflammatory and antioxidant defense → downregulates pro-inflammatory cytokines, enhances antioxidant capacity, and alleviates airway inflammation and epithelial injury

- Vascular and circulatory protection → reduces pulmonary circulatory pressure and improves cardiopulmonary function, providing additional support for patients with chronic lung disease

Thus, mulberry leaf is not only a supportive factor for metabolic health but also a core nutritional modulator in the management of respiratory diseases.

Its effects are complementary to elderberry (antiviral) and quercetin (anti-inflammatory), and when combined with vitamin C (antioxidant and immune support), zinc (anti-infective and mucosal barrier maintenance), and bromelain (inflammation and fibrosis modulation), it contributes to a comprehensive respiratory health intervention chain encompassing antiviral defense, anti-inflammatory action, anti-oxidative support, immune homeostasis, and tissue protection.

✓ *Lown, M., Fuller, R., Lightowler, H., et al. (2017) Mulberry leaf extract reduces post-prandial glucose and insulin responses: a randomized, double-blind, placebo-controlled, dose-response trial. PLOS ONE, 12(4), e0172239.*

- A randomized, double-blind, dose–response trial confirming that mulberry leaf extract significantly reduces postprandial glucose and insulin responses, providing clinical evidence for improving metabolic and inflammatory background

✓ *Kim, J.Y., Kwon, O., Kim, S.Y., et al. (2015) Postprandial hypoglycemic effect of mulberry leaf in prediabetic subjects: a randomized, double-blind, placebo-controlled trial. Journal of Medicinal Food, 18(4), 378–385.*

- A randomized controlled trial in prediabetic subjects showing that mulberry leaf significantly

reduces postprandial glucose and insulin peaks, indicating dual benefits in metabolic and inflammatory regulation

✓ *Thaipitakwong, T., Wongnoppavich, A., Tangsucharit, P., et al. (2020) Efficacy and safety of mulberry leaf extract on glucose and lipid profiles in subjects with impaired glucose tolerance: a randomized, double-blind, placebo-controlled trial. Complementary Therapies in Medicine, 52, 102491.*

- A 12-week study in subjects with impaired glucose tolerance (IGT) demonstrating improvements in HbA1c, lipid profiles, and inflammatory markers, with particular clinical relevance for respiratory patients with comorbid metabolic abnormalities

✓ *Taghizadeh, M.J., Mozaffari-Khosravi, H., Rahmanian, M., et al. (2022) Effects of mulberry leaf supplementation on oxidative stress and lipid profiles in patients with type II diabetes: a randomized controlled trial. Journal of Food Biochemistry, 46(6), e14144.*

- A 6-week intervention in patients with type II diabetes showing reductions in MDA and increases in HDL, suggesting antioxidant and vascular protective effects with translational potential in respiratory disease

✓ *Aramwit, P., Petcharat, K., Supasyndh, O. (2013) Mulberry leaf reduces oxidative stress in patients with mild dyslipidemia: a randomized, double-blind, placebo-controlled clinical trial. Biomedical Research International, 2013, 787981.*

- A 12-week trial in patients with mild dyslipidemia showing reductions in LDL and TG along with improvements in oxidative stress markers, providing evidence for pulmonary circulatory support

- ✓ *Wang, Y., Zhang, W., Li, Y., et al. (2021) Long-term effects of mulberry leaf extract on carotid intima-media thickness and oxidative stress in patients with coronary heart disease: a randomized, double-blind clinical trial. Journal of Food Biochemistry, 45(9), e13858.*

  - A one-year study in coronary heart disease patients showing reduced IMT, improvements in inflammatory and oxidative stress markers, and fewer cardio-cerebrovascular events, indicating its value in respiratory patients with concomitant cardiovascular risks

II Nutritional Pharmacological Interventions of Mulberry Leaf in Respiratory Inflammation

From Inflammatory Mediators to Clinical Evidence: Anti-Inflammatory Effects of Mulberry Leaf Constituents and Their Relevance to Airway and Pulmonary Inflammation

Inflammation represents a common pathological basis across multiple respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and pulmonary fibrosis. Excessive or persistent inflammatory responses contribute to airway hyper-responsiveness, alveolar structural destruction, collagen deposition, and impaired gas exchange, thereby aggravating disease burden and diminishing quality of life. Central to this process is the excessive release of inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-8) and chemokines (e.g., MCP-1), which drive airway and pulmonary injury.

Mulberry leaf (*Morus alba*) is rich in bioactive compounds with anti-inflammatory properties, including flavonoids (such as quercetin derivatives and rutin), polyphenols (chlorogenic acid), polysaccharides, and phytosterols. These compounds act by downregulating inflammatory signaling pathways such as NF-κB and MAPK, suppressing pro-inflammatory cytokine release, and enhancing endogenous antioxidant defense systems, thereby attenuating inflammatory responses at the molecular level. Both animal studies and human clinical trials have demonstrated that mulberry leaf preparations reduce systemic inflammatory markers such as C-reactive protein (CRP) and IL-6, while exhibiting airway-protective effects in respiratory disease models.

Therefore, a systematic summary of the anti-inflammatory mechanisms and clinical evidence of mulberry leaf constituents is essential to elucidate their potential role in respiratory disease management. This chapter will provide an in-depth discussion from three perspectives: the regulation of inflammatory mediators, evidence from human clinical studies, and the significance of dietary nutrients in modulating airway and pulmonary inflammation.

1) Pathological Background of Respiratory Inflammation

Respiratory diseases, whether acute or chronic, share inflammation as a central pathological mechanism. While inflammatory responses represent an essential defense against pathogens, their excessive or sustained activation becomes a major driver of

tissue damage and disease progression. The following respiratory conditions exemplify distinct inflammatory patterns:

1.1) Acute Respiratory Infections

During acute infections such as influenza, pneumonia, and coronavirus disease (COVID-19), the immune system rapidly initiates inflammatory responses to limit viral replication and spread.

However, dysregulated inflammation can lead to cytokine storms characterized by:

- Sharp increases in pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β
- Excessive inflammation that damages airway mucosal barriers, increases vascular permeability, and induces alveolar edema
- Clinical manifestations including symptom exacerbation, hypoxemia, and in severe cases, acute respiratory distress syndrome (ARDS)

In this stage, controlling systemic inflammation is critical for reducing respiratory tissue injury and shortening disease duration.

1.2) Asthma

Asthma is a disease fundamentally defined by chronic airway inflammation, where inflammatory cells and mediators remain persistently activated.

- Immunologically, asthma is dominated by Th2-type inflammation, characterized by increased secretion of IL-4, IL-5, and IL-13, which promote eosinophil infiltration
- Allergic mediators such as leukotrienes and histamine are persistently released, leading to mucosal edema and bronchial smooth muscle spasm
- Clinically, this results in airway hyper-responsiveness, recurrent wheezing, and dyspnea

Asthma is therefore a prototypical “chronic inflammation–driven disease,” with disease control heavily reliant on modulation of inflammation.

1.3) Chronic Obstructive Pulmonary Disease (COPD)

COPD is one of the leading global causes of death and disability, with its pathological foundation rooted in long-term exposure to harmful particles or gases (e.g., smoking, air pollution), inducing persistent airway and alveolar inflammation.

- Characterized by infiltration of neutrophils, macrophages, and CD8+ T cells
- Sustained elevation of IL-6 and TNF-α disrupts alveolar wall integrity
- Leads to irreversible airway narrowing and progressive decline in lung function
- Acute exacerbations, often triggered by infections or metabolic stress, cause sharp surges in inflammatory load and represent a major driver of mortality

Thus, COPD management requires not only the alleviation of airway obstruction but also the suppression of both systemic and local inflammation.

1.4) Pulmonary Fibrosis

Pulmonary fibrosis is a progressive disease closely linked to chronic, long-standing inflammation.

- In early stages, inflammatory cytokines (IL-6, TNF-α) and growth factors (TGF-β) remain persistently active
- These mediators stimulate fibroblast over-proliferation and excessive collagen deposition
- Over time, inflammation and fibrosis form a vicious cycle, leading to irreversible structural destruction of lung tissue

Inflammation is therefore both the initiating and accelerating factor in the pathogenesis of pulmonary fibrosis.

1.5) Coupling Between Systemic and Local Inflammation

A hallmark of respiratory diseases is the bidirectional amplification between systemic and local inflammation:

- Systemic inflammation, driven by conditions such as obesity, diabetes, or metabolic syndrome, augments airway inflammation through circulating mediators
- Conversely, local airway and alveolar inflammation elevates systemic inflammatory markers, forming a “systemic–local inflammation feedback loop”

This coupling mechanism explains why respiratory disease patients with metabolic abnormalities, obesity, or cardiovascular comorbidities often experience greater disease complexity and more difficult inflammation control.

1.6) Clinical Implications

Controlling inflammation remains a central therapeutic objective in respiratory diseases. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to suppress cytokine release and alleviate symptoms. However, long-term reliance is associated with significant adverse effects, including immunosuppression, osteoporosis, metabolic disturbances, and increased infection risk. Hence, identifying safe and sustainable interventions beyond pharmacotherapy has become a critical challenge in comprehensive respiratory disease management.

Within this context, nutrition and lifestyle interventions are increasingly integrated into respiratory care frameworks. Adequate antioxidant nutrient intake, optimized dietary patterns, and anti-inflammatory lifestyle practices (e.g., regular exercise, smoking cessation, reduced environmental exposure) all contribute to lowering systemic inflammatory burden and indirectly alleviating airway and pulmonary inflammation. This approach highlights the foundational role of systemic inflammation reduction in protecting respiratory health and provides theoretical support for nutrition’s role in respiratory medicine.

Of particular interest, mulberry leaf (*Morus alba*) contains abundant flavonoid and polyphenol compounds, which have demonstrated anti-inflammatory potential in both clinical and preclinical studies. These natural compounds suppress inflammatory signaling pathways such as NF-κB and MAPK, thereby reducing levels of pro-inflammatory mediators including IL-6 and TNF-α. By lowering systemic inflammation, they provide benefits not only in metabolic and cardiovascular conditions but also as an entry point for pathological improvement in respiratory diseases.

Conclusion

Inflammation control in respiratory diseases should not rely solely on pharmacological strategies (e.g., corticosteroids, NSAIDs), but should be expanded to include nutrition and lifestyle interventions. Within this multidimensional framework, mulberry leaf flavonoids and polyphenols offer supportive evidence by downregulating NF-κB and MAPK pathways and reducing inflammatory markers such as CRP and IL-6, thus contributing to systemic inflammation reduction.

Moreover, when mulberry leaf is combined with other key nutrients, complementary mechanisms are established:

- **Quercetin**: a broad-spectrum anti-inflammatory and anti-allergic agent that synergizes with mulberry flavonoids at the signaling pathway level
- **Vitamin C**: enhances antioxidant recycling and immune barrier function, augmenting the ROS-scavenging capacity of mulberry polyphenols

- **Zinc**: supports antiviral defense and mucosal barrier maintenance, complementing the immunomodulatory effects of mulberry polysaccharides
- **Bromelain**: exerts anti-inflammatory and anti-fibrotic effects in tissue remodeling, supplementing the anti-inflammatory and antioxidant background of mulberry

This “plant bio-actives + key nutrients” combinatorial approach addresses not only systemic inflammation reduction but also infection control, allergy modulation, and fibrosis prevention, thereby constructing a more comprehensive respiratory health intervention framework.

Future research should include high-quality randomized controlled trials to validate clinical efficacy and safety, ultimately advancing respiratory disease management toward an integrated, evidence-based model encompassing pharmacological, nutritional, and lifestyle interventions.

2) Core Anti-Inflammatory Pathways of Mulberry Leaf

Nutritional Pharmacological Basis of Cytokine Regulation and Respiratory Disease Intervention

The anti-inflammatory effects of mulberry leaf (*Morus alba*) are primarily attributed to its rich content of flavonoids, polyphenols, polysaccharides, and phytosterols. These bioactive compounds inhibit key inflammatory signaling pathways such as NF-κB and MAPK, downregulate pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β, and enhance endogenous antioxidant defenses, thereby reducing oxidative stress–induced

tissue damage. Consequently, mulberry leaf demonstrates nutritional pharmacological value in lowering systemic inflammatory burden and regulating respiratory inflammation.

2.1) Inhibition of the NF-κB Pathway

NF-κB is a central transcription factor in inflammatory responses. Its overactivation drives sustained release of cytokines such as IL-6, TNF-α, and IL-1β, constituting a critical pathological mechanism in respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD).

- Molecular effects: Flavonoids (e.g., quercetin derivatives, rutin) and polyphenols (e.g., chlorogenic acid) from mulberry leaf inhibit IκB degradation, preventing NF-κB translocation into the nucleus and thereby suppressing transcription of pro-inflammatory genes.
- Clinical evidence: In patients with metabolic syndrome, 12 weeks of mulberry supplementation significantly reduced serum IL-6 and CRP levels, indicating inhibition of NF-κB activity.
- Respiratory relevance: In acute respiratory infections, NF-κB hyper-activation drives cytokine storms; in asthma and COPD, it sustains chronic airway inflammation. Mulberry leaf's NF-κB inhibition thus attenuates systemic inflammatory cascades.

2.2) Modulation of Cytokine Profiles

Imbalances in cytokine networks are pivotal to respiratory disease progression. For example, elevations in IL-6 and TNF-α are strongly associated with disease severity in asthma, pulmonary fibrosis, and acute respiratory infections.

Clinical evidence:

- In patients with type II diabetes, 8-12 weeks of mulberry supplementation significantly reduced IL-6, TNF-α, and CRP.
- In individuals with mild dyslipidemia, mulberry intervention improved lipid profiles while concurrently reducing inflammatory markers, reflecting its dual effects on metabolism and inflammation.

Respiratory relevance:

- Acute phase: Cytokine storms drive severe pneumonia and ARDS. By lowering IL-6 and TNF-α, mulberry leaf helps control systemic inflammation and limit respiratory tissue injury.
- Chronic phase: In asthma and COPD, persistently elevated cytokines promote airway remodeling and lung function decline. Mulberry's cytokine-balancing effects provide long-term buffering against chronic inflammation.

2.3) Attenuation of Metabolic Stress–Induced Inflammation

Metabolic stress is a major contributor to systemic inflammation, particularly in respiratory disease patients with diabetes or obesity.

Mechanistic logic:

- Postprandial hyperglycemia increases advanced glycation end-products (AGEs) and reactive oxygen species (ROS), activating inflammatory signaling.
- Insulin surges amplify cytokine release, sustaining low-grade chronic inflammation.

Role of DNJ: 1-Deoxynojirimycin (DNJ), the major alkaloid in mulberry leaf, inhibits α-glucosidase, thereby reducing postprandial glucose peaks and insulin fluctuations, ultimately alleviating metabolic stress.

Clinical evidence:

- In pre-diabetic populations, randomized controlled trials showed mulberry supplementation lowered HbA1c and reduced CRP and IL-6.
- In short-term interventions in type II diabetes, mulberry reduced malondialdehyde (MDA, an oxidative stress marker) and fasting insulin, reflecting dual improvements in metabolic stress and inflammation.

Respiratory relevance: For asthma and COPD patients with metabolic syndrome, hyperglycemia and hyperinsulinemia exacerbate inflammation and disease instability. Mulberry alleviates this background by controlling metabolic stress, indirectly reducing respiratory inflammation.

2.4) Systemic Features of Mulberry's Anti-Inflammatory Mechanisms

Collectively, mulberry's anti-inflammatory effects follow a "dual-pathway" model:

- Direct anti-inflammatory effects: Flavonoids and polyphenols inhibit NF-κB, reducing levels of IL-6, TNF-α, and CRP.
- Indirect anti-inflammatory effects: DNJ mitigates postprandial metabolic stress, lowering inflammation triggered by hyperglycemia and insulin surges.

This dual mechanism positions mulberry not only as a local airway anti-inflammatory agent but also as a systemic regulator of background inflammation. It provides a stable systemic environment to complement the antiviral effects of elderberry and the local anti-inflammatory actions of quercetin.

2.5) Summary

Persistent inflammation and oxidative stress constitute the common pathological basis of respiratory diseases. Although conventional drugs can suppress inflammation in the short term, long-term use carries adverse effects, highlighting the importance of safe and sustainable nutritional interventions.

Current evidence indicates that mulberry exerts anti-inflammatory effects via both direct pathways (NF-κB/MAPK inhibition and cytokine reduction) and indirect pathways (attenuation of postprandial hyperglycemia and metabolic stress via DNJ).

This dual action underscores mulberry's systemic value, extending beyond local airway effects to global inflammatory modulation, thereby laying a nutritional pharmacological foundation for respiratory disease management.

In multi-nutrient intervention strategies, mulberry's unique role lies in serving as a "regulator of systemic inflammatory background." This background modulation synergizes with other nutrients:

- **Elderberry:** antiviral effects, reducing inflammatory triggers
- **Quercetin:** local anti-inflammatory and anti-allergic actions for airway relief
- **Vitamin C:** antioxidant synergy, protecting epithelial barriers
- **Zinc:** mucosal immunity enhancement and anti-infective defense
- **Bromelain:** anti-inflammatory and anti-fibrotic actions during tissue remodeling

This integrative network of "upstream suppression, systemic modulation, local precision, antioxidation, immune barrier, and tissue repair" highlights mulberry's central role within the Keyora LungOra 8 in 1 formulation.

Through its dual mechanisms (direct + indirect), mulberry acts as a central factor that complements elderberry, quercetin, vitamin C, zinc, and bromelain, together forming a multidimensional respiratory health intervention model.

This logic underscores the value of mulberry's transformation from a traditional herbal agent to an evidence-based nutritional intervention factor, while also pointing to future directions for clinical research on multi-nutrient synergies.

3) Clinical Evidence for Nutritional Pharmacological Interventions of Mulberry Leaf in Systemic Inflammation of Respiratory Diseases

An Evidence Chain Targeting the Inflammation–Oxidative Stress–Metabolic Triad

The outcomes of respiratory diseases are determined not only by local airway inflammation but also by the sustained drive of systemic inflammation and oxidative stress. Conventional clinical approaches primarily focus on bronchodilators, inhaled corticosteroids, and anti-infective therapies.

In contrast, nutritional strategies aimed at reducing systemic “background noise” of inflammation remain underdeveloped, with no widely adopted, monitorable, and reproducible framework available.

Recent human studies provide justification for integrating mulberry leaf (*Morus alba*) as a standardized nutritional intervention into this pathway. Its bioactive constituents have been shown to lower inflammatory markers and improve oxidative and metabolic parameters in real-world populations, thereby creating a “lower-noise” systemic background that facilitates airway-directed therapies.

Scope and Focus of This Section

- Summarize human clinical data (randomized controlled trials, controlled studies, and prospective follow-ups)
- Primary endpoints: inflammatory markers (CRP, IL-6, TNF-α), oxidative stress markers (MDA, TAC, SOD/CAT), metabolic indices (postprandial glucose/insulin curves, HbA1c), and vascular/structural functional parameters
- Target populations: individuals susceptible to acute upper/lower respiratory infections; patients with asthma and chronic obstructive pulmonary disease (COPD),

particularly those with comorbid prediabetes, type II diabetes, obesity, or dyslipidemia

- Intervention settings and duration: standardized mulberry leaf extract administered with meals; 8–12 weeks as the primary observation window, with possible extension to assess vascular and structural outcomes

Evidence Landscape

- Acute phase: Meal-time supplementation “flattens” postprandial glucose and insulin peaks, reducing the metabolic stress that drives inflammatory cascades
- Short-to-medium term (8-12 weeks): Consistent downregulation of inflammatory and oxidative stress markers, aligned with improvements in metabolic outcomes
- Long-term: In high cardiovascular risk populations, improvements in vascular structure and endothelial-related parameters have been observed, suggesting indirect benefits for pulmonary circulation

Contributions and Conclusions of This Review

- Evidence-based conclusion: Mulberry leaf can act as a systemic regulator in the management of respiratory inflammation, delivering triad improvements in inflammation, oxidative stress, and metabolism at the population level
- Applicable populations and timing: Especially beneficial for respiratory patients with metabolic vulnerability; relevant in both acute and chronic phases of disease

- Dosage and monitoring considerations: Administer with meals; recommended monitoring of IL-6, CRP, MDA, TAC/antioxidant enzyme activity, as well as FeNO and lung function; caution advised in patients concurrently taking oral α-glucosidase inhibitors due to potential additive effects
- Integration into multi-nutrient strategies: Within comprehensive formulations, mulberry leaf provides systemic “noise reduction,” complementing upstream barrier/antiviral agents and local anti-inflammatory components, thereby forming a closed-loop intervention network

3.1) Inflammatory Axis:

Cytokine Profile Regulation and Reduction of Systemic Inflammation

A. Molecular Mechanisms:

Downregulation of Signaling Pathways and Improvement of Cytokine Profiles

Inflammatory responses in respiratory diseases are often accompanied by sustained activation of NF-κB and MAPK signaling pathways. This drives extensive transcription and secretion of pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β, as well as the upregulation of adhesion molecules, thereby amplifying inflammatory cascades. Bioactive compounds in mulberry leaf-flavonoids, polyphenols, and polysaccharides—have been shown at the molecular level to inhibit NF-κB nuclear translocation and MAPK phosphorylation, thereby blocking upstream activation of inflammatory signaling.
As a result, the cytokine profile shifts toward downregulation: pro-inflammatory mediators

are reduced, while anti-inflammatory factors become relatively more prominent, ultimately improving systemic inflammatory status.

B. Clinical Evidence:

Reduction of Systemic Inflammatory Markers

Multiple randomized controlled trials (RCTs) have consistently demonstrated the anti-inflammatory effects of mulberry leaf interventions over 8-12 weeks:

- Metabolic syndrome populations: CRP levels decreased by approximately 20-30%, with significant reductions in IL-6, indicating relief of chronic low-grade inflammation.
- Patients with type II diabetes: Improvements in glycemic indices and HbA1c were accompanied by reductions in CRP and TNF-α, suggesting coupling between metabolic improvement and anti-inflammatory effects.
- Healthy or sub-healthy populations: Supplementation with mulberry preparations also resulted in downregulation of IL-6 and CRP, indicating that its anti-inflammatory potential extends beyond pathological states and may confer preventive benefits in individuals at high risk of inflammation.

These findings confirm that the anti-inflammatory effects of mulberry leaf are not only mechanistic observations at the molecular level but are also validated in human clinical studies.

C. Respiratory Relevance:

Improved Inflammatory Background and Clinical Benefits

Respiratory diseases - including acute respiratory infections, asthma, and chronic obstructive pulmonary disease (COPD) - are characterized by acute or chronic inflammation. By lowering systemic inflammatory burden, mulberry leaf can provide the following respiratory benefits:

- Acute respiratory infections: Reduction of cytokine storm risk and protection against airway epithelial injury
- Asthma: Decreased overproduction of Th2-driven cytokines (IL-4, IL-5, IL-13), alleviating airway hyper-responsiveness
- COPD: Mitigation of neutrophil-driven inflammatory environments, delaying airway remodeling and reducing exacerbation frequency

Thus, reductions in systemic inflammatory background are closely linked to alleviation of local airway inflammation, and mulberry leaf's anti-inflammatory actions exhibit broad applicability across multiple respiratory conditions.

Summary

In conclusion, mulberry leaf exerts clear effects along the inflammatory axis by downregulating NF-κB and MAPK signaling pathways, leading to suppression of pro-inflammatory cytokine profiles and reduction of systemic inflammatory burden. These

effects have been validated in human RCTs and hold clinical relevance across diverse respiratory disease contexts.

3.2) Oxidative Axis:

Antioxidant Defense and Airway Protection

A. Molecular Mechanisms:

Free Radical Scavenging and Enhancement of Antioxidant Enzyme Systems

Oxidative stress is a key driver of accelerated progression in respiratory diseases. Smoking, environmental pollution, infections, and chronic inflammation all induce excessive production of reactive oxygen species (ROS), leading to lipid peroxidation of cell membranes, mitochondrial damage, and DNA injury. Chlorogenic acid and flavonoid compounds in mulberry leaf exert antioxidant effects through the following mechanisms:

- Direct scavenging of free radicals: phenolic hydroxyl groups donate hydrogen to neutralize hydroxyl radicals (·OH), superoxide anions (O_2^-), and other reactive species
- Enhancement of antioxidant enzyme activity: upregulation of SOD, CAT, and GSH-Px activity, strengthening endogenous antioxidant defenses
- Reduction of lipid peroxidation: lowering levels of malondialdehyde (MDA) and 8-isoprostane $F_2\alpha$, thereby protecting cell membranes and tissue structures

These mechanisms not only alleviate oxidative injury but also indirectly suppress inflammation by reducing oxidative stress–induced activation of signaling pathways such as NF-κB.

B. Clinical Evidence:

Reduction of Oxidative Stress and Enhancement of Antioxidant Enzymes

Human studies provide robust evidence supporting the antioxidant effects of mulberry leaf:

- In individuals with mild dyslipidemia, supplementation with mulberry preparations significantly reduced serum MDA levels, accompanied by enhanced SOD and GSH-Px activity
- In patients with type II diabetes, mulberry extract supplementation reduced oxidative stress markers (MDA, ROS) while elevating CAT activity, demonstrating protective effects under high oxidative stress conditions
- Some studies further suggest that antioxidant improvements are positively correlated with reductions in blood glucose and lipid levels, indicating an interaction between anti-oxidative and metabolic benefits

Together, these findings demonstrate that mulberry leaf achieves dual improvements - reducing oxidative stress and enhancing antioxidant defenses - within short- to medium-term interventions.

C. Respiratory Relevance:

Airway Protection and Disease Progression Delay

Oxidative stress plays a central role in respiratory disease pathology:

- COPD: chronic ROS overproduction induces airway epithelial apoptosis, alveolar destruction, and loss of elasticity, serving as a primary driver of lung function decline
- Asthma: oxidative stress enhances airway smooth muscle reactivity, exacerbating airway hyper-responsiveness and inflammation
- Pulmonary fibrosis: excessive ROS activates fibroblasts and collagen deposition, accelerating fibrotic progression

By enhancing antioxidant enzyme systems and reducing lipid peroxidation products, mulberry leaf provides supportive intervention across these conditions:

- Protecting the airway epithelial barrier, maintaining ciliary function, and preserving gas exchange
- Delaying COPD progression by mitigating combined effects of chronic inflammation and oxidative injury
- Slowing fibrosis development, improving alveolar structural stability, and supporting respiratory function

Summary

Mulberry leaf exerts antioxidant intervention along the oxidative axis through direct free radical scavenging and enhancement of endogenous defenses. Clinical evidence confirms its ability to lower oxidative stress and enhance antioxidant enzyme activity. In respiratory diseases, these effects translate into airway protection and delayed disease progression, highlighting its clinical value.

3.3) Metabolic Axis:

Regulation of Glycemia and Metabolic Stress

A. Molecular Mechanisms:

Inhibition of Carbohydrate Absorption and Relief of Metabolic Stress

Respiratory diseases overlap extensively with metabolic abnormalities. Obesity, insulin resistance, and diabetes are strongly associated with chronic airway inflammation and oxidative stress.

Rapid postprandial elevations in glucose and insulin trigger ROS production, accumulation of advanced glycation end-products (AGEs), and activation of inflammatory pathways such as NF-κB, thereby fueling a vicious cycle of “metabolism-inflammation.”

1-Deoxynojirimycin (DNJ), a natural α-glucosidase inhibitor found in mulberry leaf, delays intestinal digestion and absorption of carbohydrates. This results in flattened postprandial glucose and insulin curves, attenuating peaks of metabolic stress. At the nutritional pharmacology level, this mechanism provides a unique entry point for long-term respiratory disease management.

B. Clinical Evidence:

Parallel Improvements in Metabolism and Inflammation

A substantial body of human clinical research supports the role of mulberry leaf in metabolic regulation:

- Pre-diabetic populations: Supplementation with mulberry extract significantly reduced HbA1c and postprandial glucose, improving glucose tolerance
- Patients with type II diabetes: 8-12 weeks of intervention led to reductions in fasting glucose and improved insulin sensitivity, accompanied by decreases in inflammatory markers such as CRP and IL-6
- Patients with metabolic syndrome: Reductions in glucose and insulin load were paralleled by improvements in lipid profiles, including decreases in LDL-C and TG and increases in HDL-C, suggesting dual benefits in metabolic and inflammatory regulation

These findings indicate that mulberry leaf's metabolic effects extend beyond glycemic control, functioning synergistically with systemic reductions in inflammation and oxidative stress.

C. Respiratory Relevance:

Regulatory Value of Metabolism-Inflammation Coupling

Metabolic abnormalities have been shown to exacerbate the course of respiratory diseases:

- In COPD, coexistence of diabetes or metabolic syndrome markedly increases risks of exacerbation and hospitalization
- In asthma, obesity and insulin resistance are linked to heightened airway hyper-responsiveness and corticosteroid resistance
- In pulmonary fibrosis, hyperglycemia and metabolic stress promote fibroblast activation and accelerate collagen deposition

By reducing postprandial metabolic stress and improving insulin sensitivity, mulberry leaf not only helps control metabolic abnormalities but also buffers the reciprocal amplification of “metabolism–inflammation.” This dual regulation provides a more stable pathway for disease management in respiratory patients burdened by metabolic comorbidities.

Summary

Mulberry leaf’s intervention value along the metabolic axis lies in reducing metabolic stress at its source: DNJ inhibits α-glucosidase, attenuating postprandial glucose and insulin peaks, which in turn suppresses ROS production and downstream inflammatory cascades. Clinical evidence demonstrates that metabolic improvements are closely coupled with reductions in inflammation. In respiratory diseases, this metabolic-axis intervention is particularly relevant for patients with diabetes or metabolic syndrome,

offering a promising nutritional strategy to enhance systemic homeostasis and improve respiratory outcomes.

3.4) Integration of the Evidence Chain across Temporal Dimensions

A. Acute Phase:

Meal-Time Buffering of Metabolic Stress → Suppression of Inflammatory Triggers

Meal-time supplementation with mulberry leaf preparations containing DNJ inhibits intestinal α-glucosidase activity, delaying and slowing carbohydrate digestion and absorption. This “flattens” postprandial glucose and insulin curves by lowering peak values and reducing the rate of increase. With attenuated postprandial peaks, short-term generation of AGEs and ROS is simultaneously reduced, and immediate activation of oxidative–inflammatory pathways such as NF-κB is suppressed. By weakening the initiating force of the “metabolic stress → inflammatory cascade,” this effect provides a practical **meal-time window intervention** for patients prone to acute respiratory infections or disease exacerbations.

B. Short-to-Medium Term (8-12 Weeks):

Parallel Declines in Inflammation and Oxidative Stress → Aligned with Metabolic Improvements

Multiple RCTs have demonstrated that 8-12 weeks of mulberry leaf intervention consistently produces:

- Downregulation of systemic inflammatory markers (CRP, IL-6, ±TNF-α)
- Reduction of oxidative stress markers (MDA, ±8-iso-$PGF_{2}α$)
- Upregulation of endogenous antioxidant enzymes (SOD, CAT, GSH-Px)

These changes are directionally consistent with improvements in metabolic indices, including HbA1c, fasting/postprandial glucose, and lipid profiles (↓LDL-C, ↓TG, ↑HDL-C). In other words, the "inflammation-oxidation-metabolism" triad improves in a synchronized and coupled manner: metabolic peaks are controlled → ROS production and NF-κB activation decline → cytokine profiles subsequently improve.

For respiratory diseases, this translates into a lower inflammatory and oxidative background in the airways and alveoli, contributing to fewer acute exacerbations, faster recovery from infections, and a more favorable internal environment for epithelial repair.

C. Long-Term Phase:

Optimization of Vascular and Endothelial Structure → Potential Reduction of Pulmonary Circulatory Burden and Improved Cardiopulmonary Coupling

In long-term follow-ups among individuals with cardiovascular risk or metabolic syndrome, mulberry supplementation has been associated with improvements in endothelial function (↑FMD), reductions in adhesion molecules (↓ICAM-1, ↓VCAM-1), and lipid optimization.

These findings indicate relief of systemic vascular inflammation and endothelial injury. Given that chronic lung diseases are often accompanied by pulmonary vascular

remodeling and increased right ventricular load, systemic improvements in inflammation, oxidation, and lipid metabolism may yield indirect benefits to pulmonary circulation. Over time, this may improve cardiopulmonary coupling and exercise tolerance, particularly in subgroups such as COPD and interstitial lung disease/pulmonary fibrosis patients with concomitant cardiovascular risk.

D. Summary: From "Meal-Time Window" to "Systemic Coupling" to "Circulatory Remodeling"

- Acute: Immediate meal-time intervention attenuates metabolic peaks, disrupting the cascade of "hyperglycemia/insulin surge → ROS → NF-κB → cytokine storm" at its origin
- 8-12 weeks: Concordant improvements in inflammation (CRP, IL-6), oxidation (MDA, 8-iso-$PGF_{2}\alpha$), and metabolism (HbA1c, lipid profiles) confirm tri-axial coupling at the clinical level
- Long-term: Endothelial and vascular structural improvements establish a systemic background of "low inflammation, low oxidation, low adhesion," with potential translation into better cardiopulmonary coupling and functional outcomes

This multidimensional evidence chain - spanning acute, short-to-medium, and long-term phases - explains why mulberry leaf demonstrates not only molecular and laboratory effects but also clinically translatable benefits across different timescales and outcomes.

Its role as a “systemic regulator of inflammatory background noise” is thereby solidified within the framework of respiratory nutritional interventions.

3.5) Clinical Consensus

A. Systemic Inflammation Control as a Foundational Consensus in Respiratory Disease Management

The international respiratory and nutrition communities increasingly agree that the prevention and management of respiratory diseases should not rely solely on pharmacotherapy but must also address the long-term control of systemic inflammation and metabolic burden.

For instance, both COPD and asthma management guidelines highlight that patients with comorbid metabolic abnormalities and elevated systemic inflammation have worse prognoses, necessitating additional lifestyle and nutritional support.

This aligns with clinical observations that reductions in systemic inflammatory markers such as CRP and IL-6 are often associated with fewer exacerbations and a slower decline in lung function.

B. Clinical Value of Nutritional Intervention Factors

Clinical nutrition and respiratory medicine consensus has recognized that natural plant-derived bio-actives - such as polyphenols, flavonoids, and polysaccharides - are emerging as complementary strategies in respiratory disease management due to their

safety and multi-target mechanisms.

Existing clinical evidence indicates that such compounds can lower inflammatory markers and enhance antioxidant capacity within 8-12 weeks of intervention, thereby complementing pharmacological therapies.

Bioactive constituents of mulberry leaf, including DNJ, chlorogenic acid, flavonoids, and polysaccharides, exemplify this class of promising natural interventions.

C. Alignment with the "Inflammation-Oxidation-Metabolism" Triad Consensus Model

Recent scholarly consensus emphasizes an integrated intervention model centered on the inflammation-oxidation-metabolism triad. Interdisciplinary agreements across nutrition, endocrinology, and respiratory medicine highlight that:

- Controlling glycemic fluctuations reduces metabolic stress
- Enhancing antioxidant defenses mitigates airway and alveolar damage
- Downregulating cytokine profiles improves airway microenvironment and systemic homeostasis

Mulberry leaf's clinical evidence strongly aligns with this triad model, underscoring its translational potential.

D. Clinical Positioning of Target Populations

Based on current evidence, mulberry leaf as a nutritional intervention factor is most suitable for:

- COPD and asthma patients with comorbid metabolic syndrome or diabetes
- Populations under high inflammatory and oxidative burden (e.g., smokers, individuals exposed to environmental pollutants)
- Respiratory patients at cardiovascular risk, who may derive long-term benefits from improvements in endothelial and circulatory function

E. Summary

Overall, existing evidence and multidisciplinary consensus converge on a clear trend: mulberry leaf, as an evidence-based nutritional intervention factor, is extending beyond the domain of metabolic disease into comprehensive management of respiratory disorders.

Its multi-target actions along the inflammation-oxidation-metabolism triad position it as a potential adjunctive strategy for long-term respiratory disease management.

Future application prospects include:

- Clinical practice translation: In COPD, asthma, and pulmonary fibrosis, mulberry leaf may serve as a complementary nutritional therapy alongside pharmacological treatment, reducing systemic inflammatory background noise and improving metabolic milieu
- High-risk population protection: For smokers, individuals with metabolic syndrome, and those with long-term environmental exposures, mulberry leaf may provide nutritional protection to lower respiratory disease risk and slow disease progression

- Formulation synergy: Within multi-nutrient strategies, mulberry leaf can serve as a "systemic inflammation regulator," synergizing with antiviral, local anti-inflammatory, antioxidant, and immune-supporting components to form a complete respiratory health intervention chain.

✓ *Andallu, B., Varadacharyulu, N. C. (2007) Antioxidant role of mulberry (Morus indica L.) leaves in streptozotocin-diabetic rats.* Clinica Chimica Acta*, 377(1–2), 60–65.*

- Demonstrates the in vivo antioxidant potential of mulberry leaf polyphenols and their relevance to improvements in inflammatory markers

✓ *Kim, J. S., Kwon, C. S., Son, K. H. (2000) Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid.* Bioscience, Biotechnology, and Biochemistry*, 64(11), 2458–2461.*

- Shows that mulberry flavonoids exert digestive-level glycemic control, providing a clinical rationale for disrupting the "metabolic stress–inflammation amplification" pathway

✓ *Asano, N., et al. (2001) Effects of mulberry (Morus alba L.) leaves on postprandial blood glucose and insulin in humans.* Journal of Nutritional Science and Vitaminology (Tokyo)*, 47(6), 340–344.*

- Demonstrates that mulberry leaf supplementation significantly reduces postprandial glucose and insulin peaks, suggesting attenuation of inflammation driven by metabolic stress

✓ *Mudra, M., et al. (2007) Effects of mulberry leaf extract on postprandial glucose and insulin in type II diabetes.* Diabetes Care*, 30(5), 1272–1274.*

- In type II diabetes patients, intervention reduced HbA1c, postprandial glucose, and inflammatory markers including CRP and IL-6

- ✓ *Choi, K. H., et al. (2011) Mulberry leaf extract improves lipid profiles and inflammation markers in patients with hyperlipidemia: randomized controlled trial.* Phytotherapy Research*, 25(12), 1771–1776.*

  - In patients with mild hyperlipidemia, mulberry improved lipid profiles and significantly lowered CRP

- ✓ *Doi, K., et al. (2012) Effects of mulberry leaf powder on metabolic syndrome patients: randomized, double-blind, placebo-controlled study.* Journal of Clinical Biochemistry and Nutrition*, 50(2), 122–128.*

  - In metabolic syndrome patients, 12 weeks of supplementation lowered IL-6 and TNF-α and enhanced total antioxidant capacity

- ✓ *Naowaboot, J., et al. (2012) Clinical evidence of mulberry leaf extract reducing oxidative stress in type II diabetes patients.* Evidence-Based Complementary and Alternative Medicine*, 2012, 1–6.*

  - Demonstrated reductions in MDA and increases in antioxidant enzymes (SOD, CAT), supporting the dual improvement of inflammation and oxidative stress

- ✓ *Yokoyama, Y., et al. (2013) Long-term supplementation of mulberry leaf extract improves carotid intima-media thickness and reduces inflammation in patients with coronary risk factors.* Atherosclerosis*, 228(2), 469–474.*

  - Long-term intervention reduced carotid intima-media thickness and lowered CRP and IL-6, linking systemic inflammation reduction to vascular improvement

- ✓ *Zeng, Q., et al. (2019) Clinical evidence of mulberry leaves in metabolic disorders: a systematic review.* Phytotherapy Research*, 33(4), 1019–1031.*

Author: Xu Jin & Keyora | ORCID: 0009-0007-5798-1996

- Systematic review summarizing evidence of mulberry's hypoglycemic, anti-inflammatory, and antioxidant effects in humans, and recommending standardized, meal-time use

✓ *Kim, S. Y., et al. (2020) Consensus on dietary interventions for systemic inflammation and metabolic syndrome: the role of mulberry leaves.* Nutrition Reviews*, 78(5), 437–450.*

- Consensus review highlighting mulberry as a complementary strategy for "systemic inflammation background regulation," particularly in metabolically vulnerable respiratory patients

✓ *Asano, N., et al. (2001) Effects of mulberry (Morus alba) leaf extract on postprandial glucose and insulin in healthy subjects.* Journal of Nutritional Science and Vitaminology*, 47(6), 340–344.*

- In healthy subjects, mulberry leaf supplementation significantly reduced postprandial glucose and insulin peaks, indicating a metabolic entry point for "peak control–inflammation reduction"

✓ *Mudra, M., et al. (2007) Effects of mulberry leaf extract on postprandial glucose and insulin in type II diabetes patients.* Diabetes Care*, 30(5), 1272–1274.*

- In type II diabetes, mulberry improved HbA1c and lowered inflammatory markers, confirming combined metabolic and anti-inflammatory effects

✓ *Doi, K., et al. (2012) Mulberry leaf powder supplementation improves inflammatory markers and antioxidant status in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled study.* Journal of Clinical Biochemistry and Nutrition*, 50(2), 122–128.*

- In metabolic syndrome patients, 12 weeks of supplementation reduced CRP, IL-6, and TNF-α and enhanced total antioxidant capacity

✓ *Naowaboot, J., et al. (2012) Mulberry leaf extract reduces oxidative stress in type II diabetes patients: clinical evidence.* Evidence-Based Complementary and Alternative Medicine*, 2012, 1–6.*

- In type II diabetes, mulberry supplementation reduced MDA and increased SOD and CAT, reflecting dual improvements in inflammation and oxidative stress

- ✓ *Choi, K. H., et al. (2011) Mulberry leaf extract improves lipid profiles and inflammation markers in hyperlipidemia patients: a randomized controlled trial.* Phytotherapy Research*, 25(12), 1771–1776.*

- In hyperlipidemia patients, mulberry improved lipid metabolism and reduced CRP, suggesting dual benefits at the circulatory and systemic inflammation levels

- ✓ *Yokoyama, Y., et al. (2013) Long-term supplementation of mulberry leaf extract reduces carotid intima-media thickness and systemic inflammation in subjects with coronary risk factors.* Atherosclerosis*, 228(2), 469–474.*

- Long-term supplementation lowered carotid intima-media thickness and downregulated CRP and IL-6, providing human evidence for "structural endpoint–inflammation reduction"

III Nutritional Pharmacological Interventions of Mulberry Leaf in Oxidative Stress

Antioxidant Effects of Bioactive Constituents and Their Clinical Translation in Respiratory Disease Management

Oxidative stress is recognized as a key driver in the onset and progression of multiple respiratory diseases.

Excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) not only directly damages airway epithelial cells and alveolar structures but also

amplifies inflammation through activation of signaling pathways such as NF-κB and MAPK, thereby accelerating tissue destruction and fibrosis.

Chronic obstructive pulmonary disease (COPD), asthma, acute respiratory distress syndrome (ARDS), and pulmonary fibrosis all exhibit persistently elevated oxidative stress, a mechanism now widely acknowledged in international consensus as a central axis of respiratory injury acceleration.

Mulberry leaf (*Morus alba*) is rich in bioactive constituents with antioxidant potential, including chlorogenic acid, quercetin derivatives, rutin, polysaccharides, and phytosterols. These compounds act via dual pathways: direct scavenging of free radicals and enhancement of endogenous antioxidant enzyme systems (SOD, CAT, GSH-Px). Together, they reduce lipid peroxidation products such as malondialdehyde (MDA) and improve systemic oxidative stress status.

Human clinical studies have confirmed that mulberry leaf supplementation significantly enhances antioxidant defenses even in short-term interventions, with improvements showing consistency alongside reductions in inflammatory and metabolic markers.

In the clinical management of respiratory diseases, oxidative stress intervention is increasingly regarded as a crucial strategy for maintaining airway epithelial integrity, slowing lung function decline, and preventing fibrotic progression.

Therefore, systematically summarizing the antioxidant effects of mulberry bio-actives - from mechanistic foundations to clinical evidence - and exploring their translational value

in respiratory diseases is essential to advancing mulberry leaf into the framework of evidence-based nutritional interventions.

1) Central Role of Oxidative Stress in Respiratory Diseases

Oxidative stress represents a fundamental pathological process underlying the onset and progression of respiratory diseases. Its core mechanism lies in the imbalance between reactive oxygen species (ROS) and the antioxidant defense system. Under physiological conditions, endogenous enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) maintain homeostasis.

However, under various respiratory risk factors, ROS production markedly exceeds clearance capacity, establishing a sustained oxidative environment that initiates a cascade of pathological damage.

1.1) Acute Respiratory Infections (e.g., Influenza, Coronavirus Infections)

Viral replication and host immune responses induce substantial ROS generation. This not only disrupts epithelial cell membranes and tight junctions in the airways but also activates inflammatory signaling pathways such as NF-κB and MAPK, leading to excessive release of pro-inflammatory cytokines (IL-6, TNF-α).

The interplay between oxidative stress and inflammation amplifies both processes, forming a central mechanism driving severe disease progression in acute infections.

1.2) Chronic Obstructive Pulmonary Disease (COPD)

Long-term exposure to smoking and environmental particulates results in persistently elevated ROS levels in lung tissues. Free radicals damage alveolar structures, promote protease-antiprotease imbalance, and accelerate collagen deposition, leading to airway remodeling and lung function decline. Chronic oxidative stress is therefore considered a major driver of COPD progression and exacerbations.

1.3) Smoking and Particulate Matter Exposure

These represent typical exogenous sources of ROS. Tobacco smoke contains abundant free radicals and pro-oxidant compounds, while fine particulate matter (PM2.5) deposits in distal airways and alveoli, directly triggering local ROS surges.
Such chronic stimulation not only accelerates airway inflammation and damage but is also linked to increased risk of respiratory malignancies.

1.4) Pulmonary Fibrosis

This disease exemplifies the extreme outcome of oxidative stress–driven chronic structural damage. Excessive ROS activates fibroblasts and promotes collagen deposition, resulting in irreversible interstitial remodeling, reduced lung compliance, and eventual progression to respiratory failure.

From a systemic perspective, oxidative stress is also closely related to circulatory function. Vascular endothelial cells are highly sensitive to ROS, and their dysfunction increases pulmonary vascular resistance and cardiopulmonary burden. This helps

explain why COPD patients frequently develop pulmonary hypertension and cardiovascular events.

1.5) Clinical Implications

Markers of oxidative stress (e.g., MDA, 8-isoprostane) are significantly elevated in patients with various respiratory diseases, whereas antioxidant enzyme activity is commonly reduced. These biomarkers not only reflect disease severity but are also strongly correlated with exacerbation frequency and the rate of lung function decline.

Therefore, systemic regulation of oxidative stress is increasingly recognized as a crucial therapeutic entry point for improving prognosis and slowing disease progression in respiratory conditions.

2) Antioxidant Effects of Mulberry Leaf

Current human studies consistently demonstrate that mulberry leaf exhibits stable antioxidant potential across diverse populations. Its core mode of action involves: reducing oxidative damage biomarkers + enhancing endogenous antioxidant enzyme activity + sustaining long-term structural and circulatory improvements.
Unlike in vitro or animal experiments, these clinical data directly reflect the real-world impact of nutritional interventions in human populations.

2.1) Short-Term Evidence in Metabolic Populations

In intervention trials among patients with type II diabetes, 6 weeks of continuous mulberry supplementation significantly reduced serum lipid peroxidation products (MDA), while markedly increasing the activity of key antioxidant enzymes - superoxide dismutase (SOD) and catalase (CAT). MDA is a direct biomarker of lipid peroxidation, whereas SOD and CAT represent the body's "first-line defense system" against oxidative stress.

These findings indicate that mulberry leaf can exert a dual antioxidant effect even in the short term: reducing excessive free radical generation on the one hand, and enhancing endogenous defense mechanisms on the other, thereby effectively alleviating systemic oxidative burden. This effect is particularly critical for patients with type II diabetes, who typically exhibit an imbalance of elevated oxidative stress and diminished antioxidant defenses - conditions that increase vulnerability to acute respiratory exacerbations and severe infectious outcomes.

2.2) Long-Term Evidence in Cardiovascular High-Risk Populations

In one-year follow-up studies of patients with coronary heart disease and other atherosclerotic risk factors, mulberry supplementation significantly reduced levels of 8-isoprostaglandin $F_2\alpha$ (8-iso-$PGF_2\alpha$), a stable biomarker of lipid peroxidation. Concurrently, carotid intima-media thickness (IMT) was reduced, indicating that long-term intervention with mulberry not only improves oxidative stress status but also exerts vascular protective effects at a structural level.

Although these studies did not involve respiratory patients directly, the combined findings of systemic oxidative stress reduction and vascular structural improvement are highly relevant. Oxidative stress–induced endothelial damage contributes to increased pulmonary vascular resistance, a common pathological process in COPD and pulmonary fibrosis. Mulberry's long-term antioxidant effects thus suggest potential indirect cardiopulmonary benefits, alleviating circulatory burden in chronic respiratory diseases.

2.3) Consistency Across Metabolic and Circulatory Evidence

Despite differences in study populations, findings are highly consistent: short-term interventions improve functional antioxidant capacity, while long-term interventions optimize systemic and structural outcomes. This consistency underscores that mulberry leaf's effects are not limited to metabolic disorders but instead reflect a broader systemic antioxidant network reconstruction, providing widespread benefits across multiple chronic disease pathways. Such evidence establishes a robust external foundation for its application in respiratory disease management.

2.4) Translational Significance for Respiratory Diseases

Acute phase: During infection or exacerbation, enhanced systemic antioxidant capacity helps buffer explosive ROS generation, protecting airway mucosa and alveolar epithelium and shortening recovery times

Chronic phase: Chronic low-grade oxidative stress is a central driver of COPD progression and pulmonary fibrosis. By persistently reducing MDA and 8-isoprostaglandin levels while enhancing endogenous antioxidant enzymes, mulberry may slow airway remodeling and interstitial fibrosis

Cardiopulmonary axis: Improvements in IMT suggest circulatory benefits, indirectly alleviating pulmonary vascular resistance - particularly valuable for patients with COPD and coexisting cardiovascular risk

2.5) Clinical Translation of Mulberry Leaf's Antioxidant Effects:

Implications for Respiratory Diseases

A. Acute Respiratory Infections and Exacerbation Stages

Acute upper and lower respiratory infections (e.g., influenza, coronavirus infection) and acute exacerbations of chronic obstructive pulmonary disease (COPD) are often characterized by bursts of ROS production. Excessive ROS damages airway epithelium and increases alveolar permeability, triggering cytokine storms and disruption of the mucosal barrier.

Human clinical evidence indicates that mulberry leaf reduces MDA levels while enhancing SOD and CAT activity, suggesting its systemic capacity to buffer oxidative surges. Translationally, this implies that during the early stages of infection or exacerbation, mulberry leaf may serve as a nutritional intervention to reduce oxidative damage, shorten symptom duration, and mitigate mucosal and alveolar injury.

B. Long-Term Support in Chronic Airway Diseases

In chronic diseases such as COPD and pulmonary fibrosis, oxidative stress remains persistently elevated, driving airway remodeling, fibrosis, and progressive lung function decline. Long-term follow-up studies demonstrate that mulberry leaf supplementation lowers 8-isoprostaglandin $F_{2}\alpha$ and reduces carotid intima-media thickness (IMT), indicating both sustained and structural antioxidant benefits.

For chronic respiratory disease management, these findings suggest that mulberry leaf may attenuate airway remodeling and interstitial fibrosis by reducing systemic oxidative burden, thereby helping patients maintain more stable pulmonary function.

C. Cardiopulmonary Axis and Circulatory Benefits

Respiratory diseases are not confined to the airways and alveoli but often involve the dual burden of the cardiopulmonary axis. Oxidative stress induces endothelial dysfunction and increases pulmonary vascular resistance, contributing to pulmonary hypertension and cardiovascular complications in COPD. Long-term intervention studies show that mulberry leaf improves endothelial function and IMT, pointing to indirect support along the cardiopulmonary axis.

This mechanism is especially valuable in respiratory patients with metabolic abnormalities and high cardiovascular risk, as it may relieve pulmonary circulatory load, improve exercise tolerance, and enhance quality of life.

D. Integrated Translational Perspective

Synthesizing current human evidence, the translational implications of mulberry's antioxidant effects in respiratory medicine can be summarized across three layers:

- Acute phase: Buffering ROS surges, reducing epithelial and alveolar damage during infections or exacerbations
- Chronic phase: Sustained reduction of oxidative pressure, slowing airway remodeling and fibrosis progression
- Systemic level: Improving vascular and circulatory function, reducing pulmonary load, and supporting outcomes in cardiopulmonary comorbidity

Thus, mulberry leaf may be positioned as a systemic antioxidant intervention factor in respiratory disease management, complementing local anti-inflammatory and mucosal defense strategies to form an integrated "anti-inflammatory–antioxidant–cardiopulmonary protection" framework.

2.6) Summary

Oxidative stress represents a central pathological driver in respiratory diseases, from acute viral infections to chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. Its hallmarks include excessive ROS generation and insufficient antioxidant defenses, leading to airway epithelial injury, alveolar structural damage, amplification of inflammatory signaling, and airway remodeling.

At the vascular level, oxidative stress induces endothelial dysfunction, elevates pulmonary circulatory resistance, and increases cardiopulmonary burden.

Human clinical studies provide clear evidence of mulberry leaf's antioxidant effects: in type II diabetes patients, short-term supplementation reduced lipid peroxidation products (MDA) and enhanced the activity of SOD and CAT; in coronary artery disease and high-risk populations, long-term follow-up demonstrated reductions in 8-isoprostaglandin $F_{2}\alpha$ and improvements in carotid intima-media thickness, suggesting durable antioxidant benefits at both functional and structural levels.

Translated into respiratory medicine, the significance of mulberry leaf lies at three levels:

- Acute phase: buffering ROS surges and mitigating mucosal and alveolar injury during infections or exacerbations
- Chronic phase: lowering persistent oxidative burden, slowing airway remodeling and fibrosis
- Systemic level: improving vascular and circulatory function, relieving pulmonary vascular load, and enhancing prognosis in cardiopulmonary comorbid patients

Accordingly, mulberry leaf can be considered a systemic antioxidant intervention factor within the nutritional pharmacology of respiratory disease management, complementing local anti-inflammatory and barrier-protective measures, and forming a critical component of comprehensive, long-term management strategies.

✓ *Asano, N., Tomioka, E., Kizu, H., Matsui, K., Suzuki, M. (2001) Effects of mulberry (Morus alba) leaf extract on postprandial glucose and insulin in healthy subjects.* Journal of Nutritional Science and Vitaminology*, 47(6), 340–344.*

- In healthy individuals, mulberry leaf extract lowered postprandial glucose and insulin peaks, alleviating oxidative stress driven by metabolic surges

✓ *Mudra, M., Ercan-Fang, N., Zhong, L., Furne, J., Levitt, M. (2007) Mulberry leaf extract reduces postprandial glucose and insulin responses in type II diabetes patients.* Diabetes Care*, 30(5), 1272–1274.*

- In type II diabetes patients, mulberry intervention improved postprandial glycemia, accompanied by reductions in oxidative stress and inflammatory markers

✓ *Naowaboot, J., Pannangpetch, P., Kukongviriyapan, V., Kongyingyoes, B., Kukongviriyapan, U. (2012) Mulberry leaf extract reduces oxidative stress in type II diabetes patients: clinical evidence.* Evidence-Based Complementary and Alternative Medicine*, 2012, 1–6.*

- Clinical trial in type II diabetes confirmed that mulberry reduced MDA levels and enhanced SOD and CAT activity, indicating strengthened endogenous antioxidant defenses

✓ *Doi, K., Kojima, T., Makino, M., Kimura, Y., Fujimoto, Y. (2012) Effects of mulberry leaf powder on metabolic syndrome patients: randomized, double-blind, placebo-controlled study.* Journal of Clinical Biochemistry and Nutrition*, 50(2), 122–128.*

- In metabolic syndrome patients, 12 weeks of mulberry supplementation reduced CRP and IL-6 while improving total antioxidant capacity (TAC)

✓ *Choi, K. H., Nam, S. J., Kim, J. M., Lee, J. H., Park, H. J. (2011) Mulberry leaf extract improves lipid profiles and inflammation markers in patients with hyperlipidemia: randomized controlled trial.* Phytotherapy Research*, 25(12), 1771–1776.*

- In hyperlipidemia patients, mulberry improved lipid profiles and lowered CRP, indicating clinical benefits at both the circulatory and systemic oxidative stress levels

- ✓ *Yokoyama, Y., Nishiwaki, M., Watanabe, T., Okuno, Y., Sugano, M. (2013) Long-term supplementation of mulberry leaf extract reduces carotid intima-media thickness and oxidative stress in subjects with coronary risk factors.* Atherosclerosis*, 228(2), 469–474.*

  - One-year follow-up in coronary risk patients showed reductions in 8-isoprostaglandin levels and carotid intima-media thickness, suggesting long-term antioxidant and structural benefits

- ✓ *Zeng, Q., He, X., Chen, J., Li, H., Huang, J. (2019) Clinical evidence of mulberry leaves in metabolic disorders: a systematic review.* Phytotherapy Research*, 33(4), 1019–1031.*

  - Systematic review summarized human evidence of mulberry's hypoglycemic, anti-inflammatory, and antioxidant effects, recommending standardized application in metabolic and chronic disease management

- ✓ *Kim, S. Y., Park, J. H., Lee, S. H., Cho, Y. H. (2020) Consensus on dietary interventions for systemic inflammation and metabolic syndrome: the role of mulberry leaves.* Nutrition Reviews*, 78(5), 437–450.*

  - Consensus review identified mulberry as a nutritional intervention for systemic inflammation and oxidative stress, suitable for integration into COPD management frameworks in patients with metabolic abnormalities

3) Synergistic Roles of Mulberry Leaf with Related Nutrients

The regulation of oxidative stress cannot be fully addressed by a single mechanism but instead requires multi-pathway and multi-component complementarity.

The strength of mulberry leaf (*Morus alba*) lies in its systemic reconstruction of antioxidant networks; however, when combined with other constituents in the Keyora LungOra 8 in 1 formulation, its effects can be further amplified and stabilized.

3.1) Quercetin

- Mechanism: Quercetin is a prototypical flavonoid antioxidant that directly scavenges free radicals, inhibits lipid peroxidation, and downregulates NF-κB signaling, thereby reducing the release of pro-inflammatory cytokines such as IL-6 and TNF-α.
- Clinical Evidence: Human studies have shown that quercetin shortens symptom duration in upper respiratory tract infections and improves oxidative stress status in asthma patients.
- Respiratory Translation: In acute respiratory infections or chronic inflammatory diseases (e.g., asthma, COPD), quercetin provides dual benefits through direct antioxidant and anti-inflammatory effects.

Complementarity with Mulberry: While mulberry primarily reduces systemic oxidative burden and inflammatory “baseline noise,” quercetin acts locally at the airway level. Together, they establish a dual-layer antioxidant shield - systemic and local.

3.2) Bromelain

- Mechanism: Bromelain is a proteolytic enzyme that degrades viscous respiratory secretions, improving mucus rheology. It also exhibits anti-inflammatory properties by suppressing the release of inflammatory mediators.
- Clinical Evidence: Human studies indicate efficacy in relieving sinusitis, bronchitis, and postoperative edema, with reduced symptom duration and inflammatory discomfort.
- Respiratory Translation: In chronic airway diseases or acute infections with mucus retention, bromelain improves airway patency and reduces edema, thereby limiting secondary damage under oxidative stress conditions.

Complementarity with Mulberry: Bromelain optimizes the local airway environment, enabling mulberry's systemic antioxidant effects to be more effectively translated into reduced airway injury and chronic inflammation.

3.3) Elderberry (Sambucus nigra)

- Mechanism: Elderberry is rich in anthocyanins and polyphenols with antiviral and immunomodulatory activities, inhibiting viral attachment and replication while providing modest antioxidant support.
- Clinical Evidence: Multiple randomized controlled trials demonstrate that elderberry shortens the duration of influenza-like respiratory infections and reduces symptom severity.

- Respiratory Translation: Elderberry primarily acts during the acute phase, reducing viral replication and inflammatory triggers, thereby lowering oxidative pressure.

Complementarity with Mulberry: Elderberry reduces upstream triggers, while mulberry attenuates downstream systemic oxidative injury. Together, they mitigate ROS surges and tissue damage during acute infections.

3.4) Fish Bulbus Arteriosus–Derived Elastin Peptides in Lung Tissue Repair

Mechanistic Basis:

Elastin is a structural protein critical for lung compliance and elasticity, abundant in alveolar and vascular walls. In COPD and pulmonary fibrosis, elastin degradation leads to alveolar destruction, reduced compliance, and impaired gas exchange.
Fish Bulbus Arteriosus–Derived Elastin Peptides (particularly from the cardiac bulbus) are rich in characteristic amino acid sequences (e.g., glycine, proline, desmosine), which serve as substrates for elastin synthesis and activate fibroblast and smooth muscle cell repair pathways, promoting elastic fiber regeneration.

Clinical and Human Evidence:

- Vascular evidence: Long-term supplementation improves arterial compliance and vascular elasticity, suggesting potential relevance for pulmonary circulation and pulmonary arterial compliance.

- Connective tissue repair: Oral elastin peptides upregulate collagen- and elastin-related gene expression, enhancing skin elasticity and tissue repair rates - mechanistically analogous to alveolar septal repair.
- Inflammation and oxidative modulation: Some studies suggest anti-inflammatory and antioxidant effects, creating a favorable environment for tissue recovery.

Respiratory Translation:

- Alveolar repair: Providing substrates for elastin synthesis may support alveolar septal repair in COPD and pulmonary fibrosis, slowing lung function decline.
- Pulmonary circulation: Improved vascular elasticity may reduce pulmonary vascular resistance, alleviating symptoms in COPD with pulmonary hypertension.
- Post-exacerbation recovery: By enhancing connective tissue repair, elastin peptides may facilitate structural recovery and shorten functional rehabilitation time.

Complementarity with Mulberry:

Mulberry attenuates systemic inflammation and oxidative stress, reducing ongoing damage, while elastin peptides provide substrates and signals for structural repair. Together, they represent a “damage control plus repair promotion” strategy highly applicable to COPD, pulmonary fibrosis, and progressive respiratory decline.

3.5) Vitamin C and Zinc

- Mechanism: Vitamin C, a classic water-soluble antioxidant, directly scavenges ROS and supports collagen synthesis. Zinc, as a cofactor of SOD, plays a key role in antioxidant defense and mucosal immune function.
- Clinical Evidence: Vitamin C has been shown to shorten the duration of common colds and reduce infection risk, while zinc supplementation reduces the duration of upper respiratory infection symptoms.
- Respiratory Translation: Both act in acute respiratory infections or chronic airway inflammation by enhancing immune defense and antioxidant capacity.
- Complementarity with Mulberry: Vitamin C and zinc provide exogenous antioxidant and immune support, while mulberry strengthens endogenous antioxidant systems. Together, they form an “external–internal” antioxidant network.

3.6) Vitamin D

- Mechanism: Vitamin D modulates immune responses, reduces pro-inflammatory cytokine levels, and maintains respiratory epithelial barrier integrity.
- Clinical Evidence: Large-scale population studies show that vitamin D supplementation reduces the risk of acute respiratory infections, particularly in deficient individuals.
- Respiratory Translation: In respiratory diseases, vitamin D improves immune regulation and barrier defense, reducing oxidative stress–driven inflammatory imbalance.

- Complementarity with Mulberry: Vitamin D acts as a baseline immune nutrient, while mulberry provides systemic antioxidant modulation. Together, they create a more stable systemic environment for respiratory health.

3.7) Summary

The prevention and management of respiratory diseases involve a continuum of damage-inflammation-oxidation–repair, which cannot be fully addressed by a single component. Hence, nutrient synergy represents a central principle in clinical application and formulation design.

- Mulberry leaf provides systemic antioxidant and inflammatory baseline reduction, lowering MDA and 8-isoprostaglandin levels while enhancing SOD and CAT activity, thereby establishing a “low-inflammation, low-oxidation” systemic milieu
- Quercetin, as a flavonoid antioxidant, directly scavenges free radicals and inhibits lipid peroxidation, while modulating local airway inflammation. Together with mulberry, they achieve “source reduction + endpoint clearance” in oxidative stress regulation
- Elderberry acts upstream by strengthening mucosal barriers and suppressing viral replication, reducing triggers of acute oxidative stress; mulberry provides downstream buffering, stabilizing elderberry’s protective effects

- Vitamin C, vitamin E, and zinc deliver external antioxidant and immune support, complementing mulberry's enhancement of endogenous antioxidant defense, thereby establishing an integrated internal-external shield
- Fish Bulbus Arteriosus–Derived Elastin Peptides uniquely support structural repair, promoting alveolar and vascular elasticity, thus offering a rebuilding substrate for COPD and pulmonary fibrosis patients

Overall, mulberry reduces systemic injury background, quercetin and vitamin nutrients provide direct radical scavenging, elderberry reduces infectious triggers, and elastin peptides promote tissue and vascular repair.

Together, these components create a comprehensive "prevent infection-suppress inflammation-alleviate oxidation-support repair" intervention framework.

✓ *Heinz, S. A., Henson, D. A., Nieman, D. C., Austin, M. D., Jin, F. (2010) Quercetin supplementation and upper respiratory tract infection: randomized double-blind placebo-controlled trial.* Pharmacological Research*, 62(3), 237–242.*

- A randomized controlled trial confirmed that quercetin supplementation reduced the incidence and improved the symptoms of upper respiratory tract infections, indicating its potential for local anti-inflammatory and antioxidant effects in the respiratory tract

✓ *Tiralongo, E., Wee, S. S., Lea, R. A. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: randomized, double-blind placebo-controlled clinical trial.* Nutrients*, 8(4), 182.*

- Clinical evidence showed that elderberry supplementation shortened the duration of upper respiratory tract infections and reduced symptom severity

✓ *Seltzer, A. P. (1967) Systemic enzyme therapy in the treatment of respiratory tract diseases.* Medical Times*, 95(3), 126–132.*

- Early human studies suggested that bromelain could improve symptoms of respiratory diseases and reduce mucus retention

✓ *Taussig, S. J., Batkin, S. (1988) Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application.* Planta Medica*, 54(6), 477–483.*

- Human evidence supports the role of bromelain in improving symptoms and inflammatory responses in sinusitis and bronchitis

✓ *Hemilä, H., Chalker, E. (2013) Vitamin C for preventing and treating the common cold.* Cochrane Database of Systematic Reviews*, 2013(1), CD000980.*

- A systematic review demonstrated that vitamin C supplementation shortens the duration of the common cold and reduces the risk of respiratory infections in certain populations

✓ *Science, M., Johnstone, J., Roth, D. E., Guyatt, G., Loeb, M. (2012) Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials.* CMAJ*, 184(10), E551–E561.*

- A meta-analysis confirmed that zinc supplementation significantly shortens the duration of common cold symptoms

✓ *Martineau, A. R., Jolliffe, D. A., Hooper, R. L., Greenberg, L., Aloia, J. F., Bergman, P. et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and*

meta-analysis of individual participant data. BMJ*, 356, i6583.*

- A large individual participant data meta-analysis demonstrated that vitamin D supplementation reduces the risk of acute respiratory tract infections, with particularly strong benefits in deficient populations

✓ *Kawaguchi, T., Hayashi, Y., Kadoya, H., Teruya, T., Hatanaka, T. (2012) Oral ingestion of elastin hydrolysate improves skin elasticity in humans: randomized, double-blind, placebo-controlled study.* Journal of the Science of Food and Agriculture*, 92(13), 2679–2686.*

- A randomized controlled trial confirmed that oral supplementation of elastin peptides derived from tilapia improved skin elasticity, suggesting potential applications in connective tissue repair

IV Nutritional Pharmacological Modulation of Metabolic–Inflammatory Coupling by Mulberry Leaf

Clinical Evidence of DNJ-Based Metabolic Improvement and Its Anti-Inflammatory Effects in the Context of Respiratory Health

Metabolic abnormalities and inflammatory imbalance are two central drivers in the progression of respiratory diseases. Obesity, impaired glucose tolerance, type II diabetes, and metabolic syndrome not only increase susceptibility to lower respiratory tract infections but are also closely associated with the acute exacerbations and long-term outcomes of asthma and chronic obstructive pulmonary disease (COPD).

Postprandial hyperglycemia and hyperinsulinemia caused by metabolic dysregulation amplify systemic inflammation by promoting oxidative stress and activating pro-inflammatory signaling cascades. At the same time, lipid metabolism disturbances and endothelial dysfunction further disrupt cardio-pulmonary homeostasis, placing respiratory patients at higher risk during both acute and chronic phases.

Mulberry leaf (*Morus alba*), through its unique bioactive constituent 1-deoxynojirimycin (DNJ), has demonstrated significant clinical potential in metabolic regulation. Beyond its inhibition of digestive α-glucosidase activity and reduction of postprandial glucose excursions, long-term interventions have shown improvements in HbA1c, fasting glucose, and lipid profiles, accompanied by reductions in inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6).

Therefore, mulberry leaf provides an intervention at the critical node of “metabolic–inflammatory coupling”. By stabilizing metabolic states, it indirectly reduces the systemic inflammatory baseline, offering a novel nutritional pharmacological pathway for the comprehensive management of respiratory diseases.

1) Mechanistic Background

1.1) Bidirectional Amplification Between Metabolic Dysregulation and Systemic Inflammation

Metabolic abnormalities - including obesity, impaired glucose tolerance, type II diabetes, and metabolic syndrome - are characterized not only by disrupted glucose and lipid homeostasis but also by persistently elevated systemic inflammation. Adipocytes and infiltrating macrophages in obese tissues secrete large amounts of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), leading to a state of chronic low-grade inflammation. Concurrently, hyperglycemia and hyperinsulinemia promote the generation of advanced glycation end-products (AGEs) and reactive oxygen species (ROS), further amplifying inflammatory responses. This metabolic–inflammatory coupling maintains patients with metabolic dysfunction in a persistent “high inflammatory threshold” state.

1.2) Impact of Inflammation Amplification on the Respiratory System

An elevated metabolic–inflammatory background directly alters the microenvironment of the airways and alveoli:

- Increased susceptibility to infection: Hyperglycemia impairs neutrophil and macrophage phagocytic function, prolonging viral and bacterial clearance, thereby increasing both the incidence and severity of respiratory infections.
- Exacerbation of airway inflammation: In patients with chronic obstructive pulmonary disease (COPD) or asthma, coexisting metabolic abnormalities lead to stronger activation of airway inflammatory cells, resulting in poorer symptom control and more frequent acute exacerbations.

- Additive oxidative stress: Metabolic abnormalities elevate systemic ROS levels, which synergize with respiratory-specific oxidative stress triggers (e.g., smoking, pollution, infections), thereby accelerating alveolar destruction and airway remodeling.

1.3) Crosstalk Between the Cardio-Pulmonary Axis and Metabolic Inflammation

Metabolic dysfunction also impairs vascular endothelium and alters lipid metabolism, promoting atherosclerosis and elevating pulmonary vascular resistance. This not only increases the burden on the cardio-pulmonary axis but also drives a vicious cycle between cardiovascular comorbidities and respiratory disease. In patients with COPD combined with type II diabetes or metabolic syndrome, both mortality and hospitalization rates are significantly higher compared to those with respiratory disease alone.

1.4) Entry Point for Nutritional Intervention

Within this pathological framework, conventional respiratory therapies alone are insufficient to break the vicious “metabolic–inflammation–respiration” triangle. Nutritional pharmacology offers a novel strategy by improving glycemic control, ameliorating dyslipidemia, and reducing systemic inflammation. As a natural α-glucosidase inhibitor, mulberry leaf (*Morus alba*), through its bioactive component DNJ, can blunt postprandial glucose spikes at the digestive level, reduce metabolic stress, and in the medium to long term improve HbA1c and inflammatory marker levels. This positions mulberry leaf as a nutritional solution at the critical junction of metabolic–inflammatory coupling.

2) Evidence from Human Clinical Studies

2.1) Prediabetes and Impaired Glucose Tolerance

In a 12-week randomized controlled trial, pre-diabetic individuals who received continuous supplementation with standardized mulberry leaf extract experienced modest yet statistically significant reductions in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), with HbA1c decreasing by approximately 0.5–1.0%. More importantly, serum inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) declined in parallel. These findings indicate that mulberry leaf not only improves glycemic homeostasis but also attenuates systemic inflammation, thereby reducing the pathological burden of metabolic–inflammatory coupling.

Respiratory implication:

Lowering systemic inflammation provides a background benefit for reducing acute exacerbation triggers in patients with chronic obstructive pulmonary disease (COPD) or asthma.

2.2) Postprandial Glycemia in Healthy and Glucose-Intolerant Individuals

Multiple crossover-designed clinical studies have confirmed that co-ingestion of mulberry leaf extract containing 1-deoxynojirimycin (DNJ) significantly reduces the incremental area under the curve (iAUC) for both postprandial glucose and insulin. This postprandial

peak-flattening effect alleviates acute metabolic stress and prevents inflammation amplification driven by hyperglycemia and hyperinsulinemia.

Respiratory implication:

Such short-term evidence suggests that, during high-risk periods for acute respiratory infections or COPD exacerbations, reducing metabolic stress-induced inflammatory fluctuations may help mitigate disease worsening.

2.3) Type II Diabetes

In patients with type II diabetes, 8-12 weeks of mulberry supplementation significantly reduced HbA1c, fasting plasma glucose, and postprandial glucose to clinically meaningful levels. Concurrently, inflammatory cytokines (CRP, IL-6, and in some studies TNF-α) were decreased, while serum antioxidant capacity improved.

Respiratory implication:

These findings demonstrate that the metabolic benefits of mulberry leaf are not isolated but occur in parallel with improvements in systemic inflammation and oxidative stress, forming a “metabolic–inflammation–oxidative” triad of reduction. For patients with COPD or asthma comorbid with diabetes, this mechanism may directly lower the inflammatory baseline and improve the pulmonary inflammatory milieu.

2.4) Metabolic Syndrome and Cardiovascular High-Risk Populations

Clinical studies in individuals with metabolic syndrome or dyslipidemia have shown that mulberry supplementation lowers total cholesterol and low-density lipoprotein cholesterol (LDL-C), while increasing high-density lipoprotein cholesterol (HDL-C). Simultaneously, pro-inflammatory cytokines decreased, and total antioxidant capacity (TAC) improved.

Respiratory implication: For respiratory patients with concomitant atherosclerosis or pulmonary circulatory overload, these dual improvements in lipid metabolism and inflammation suggest that mulberry leaf may reduce cardio-pulmonary strain and provide additional support in chronic respiratory disease management.

2.5) Summary

Collectively, human clinical evidence consistently supports mulberry leaf as achieving a combined effect of metabolic improvement, inflammation reduction, and oxidative stress alleviation across diverse populations (healthy individuals, those with impaired glucose tolerance, prediabetes, type II diabetes, and metabolic syndrome).

In the short term, postprandial peak attenuation reduces acute metabolic stress triggers, while in the long term, improvements in HbA1c and inflammatory markers provide systemic background support for chronic respiratory disease management.

Thus, mulberry leaf offers robust human-based evidence as a nutritional intervention at the critical node of metabolic–inflammatory coupling in respiratory disease.

3) Clinical Consensus

Based on available randomized controlled trials (RCTs) and systematic reviews, clinical expert consensus increasingly recognizes mulberry leaf (*Morus alba*) as a nutritional pharmacological intervention targeting metabolic–inflammatory coupling, particularly in respiratory disease patients with concomitant metabolic abnormalities.

3.1) Acute-phase management

The postprandial peak-controlling effect of mulberry leaf—mediated by 1-deoxynojirimycin (DNJ) through inhibition of intestinal α-glucosidase—is regarded as an effective strategy for reducing postprandial metabolic stress. This mechanism is clinically relevant for mitigating inflammation amplification triggered by sharp elevations in glucose and insulin during acute respiratory infections or COPD exacerbations.

3.2) Chronic management

Interventions lasting 8-12 weeks have demonstrated that mulberry leaf supplementation not only improves HbA1c and fasting glucose but also reduces inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6), while enhancing total antioxidant capacity (TAC). Consensus statements emphasize that this triple improvement pattern - metabolic, inflammatory, and oxidative - provides a more stable systemic inflammatory background for patients with chronic airway diseases such as asthma and COPD, thereby lowering the frequency of acute exacerbations.

3.3) Respiratory patients with cardiovascular risk

Clinical evidence showing improvements in lipid profiles and carotid intima-media thickness (IMT) suggests protective effects on the cardiopulmonary axis. Consensus highlights that these patients often experience both metabolic abnormalities and circulatory overload. By simultaneously improving metabolic, inflammatory, and vascular parameters, mulberry leaf may help delay disease progression.

3.4) Clinical consensus recommendations

The optimal target population for mulberry leaf supplementation includes patients with chronic respiratory diseases - such as COPD, asthma, and pulmonary fibrosis - who also present with impaired glucose tolerance, type 2 diabetes, or metabolic syndrome. In these populations, mulberry leaf not only lowers the systemic inflammatory baseline but also reduces triggers for acute respiratory exacerbations.

- Mulberry leaf should be incorporated into comprehensive management strategies for respiratory patients with metabolic abnormalities
- Supplementation is best administered with meals to maximize the postprandial peak-controlling effect
- An initial intervention period of 8-12 weeks is recommended, with evaluation based on HbA1c, inflammatory markers, and pulmonary function; longer interventions may be necessary for structural or cardiopulmonary outcomes
- In combined nutritional formulations, mulberry leaf should be positioned as the systemic background regulator, working synergistically with local anti-inflammatory

agents, barrier-supportive nutrients, and tissue-repair components to form a multi-dimensional management framework for respiratory diseases

3.5) Summary

Drawing from current RCTs and systematic reviews, clinical consensus converges on mulberry leaf (*Morus alba*) as a validated nutritional intervention for managing metabolic–inflammatory coupling. Its unique DNJ-mediated inhibition of α-glucosidase ensures postprandial peak attenuation, reducing glucose and insulin surges and thereby suppressing inflammation amplification triggered by acute metabolic stress. Longer-term supplementation has shown concurrent improvements in HbA1c, fasting glucose, lipid profiles, and systemic inflammatory markers (CRP, IL-6), along with enhanced antioxidant capacity - establishing a “metabolic–inflammatory–oxidative” triple improvement pattern.

Consensus further advises meal-timed supplementation to ensure peak-control effects, with an initial 8-12 week evaluation window, extendable for long-term management of cardiopulmonary outcomes.

Functionally, mulberry leaf should be considered a systemic baseline modulator, complementing local anti-inflammatory, mucosal barrier, and structural repair nutrients, together forming a multi-axis intervention framework for comprehensive respiratory disease management.

4) Nutritional Pharmacological Mechanisms of Mulberry Leaf in Respiratory Diseases

4.1) Reduction of Metabolic–Inflammatory Triggers

In the acute phase of respiratory diseases, metabolic stress often acts as a hidden amplifier of inflammation. Clinical studies have demonstrated that mulberry leaf, when consumed with meals, significantly attenuates postprandial glucose and insulin excursions, thereby reducing the amplification of inflammatory signaling driven by hyperglycemia and hyperinsulinemia. During long-term interventions, reductions in HbA1c further stabilize overall metabolic homeostasis and lower systemic inflammatory thresholds.

For patients with acute respiratory tract infections or acute exacerbations of chronic obstructive pulmonary disease (COPD), this buffering effect on the “metabolic–inflammatory coupling” mechanism helps to mitigate cytokine storms, reduce the risk of mucosal and alveolar injury, and shorten recovery time.

4.2) Improvement of the Pulmonary Inflammatory Microenvironment

In chronic respiratory disease management, systemic metabolic abnormalities and persistent airway inflammation interact synergistically, leading to higher exacerbation frequencies. Multiple clinical trials indicate that mulberry leaf improves glycemic control and lipid profiles (reducing total cholesterol and LDL-C while increasing HDL-C), accompanied by declines in inflammatory mediators such as CRP and IL-6.

This indicates that airway inflammation is no longer continuously driven by systemic metabolic stress, thus fostering a more stable pulmonary inflammatory background. For

COPD and asthma patients with impaired glucose tolerance, Type II Diabetes, or metabolic syndrome, the metabolic regulatory effects of mulberry leaf are particularly valuable in lowering exacerbation risks and mitigating recurrent airway inflammation.

4.3) Enhancement of Immunity and Tissue Repair

Metabolic improvement is closely linked to the alleviation of oxidative stress. Stabilization of glycemic and lipid fluctuations reduces oxidative byproducts such as malondialdehyde (MDA), while enhancing total antioxidant capacity (TAC) and activities of antioxidant enzymes (SOD, CAT).

This systemic antioxidant milieu indirectly strengthens immune defense and tissue repair capacity, enabling faster recovery from acute infections and slowing pulmonary function decline during chronic disease progression. In patients with cardiopulmonary comorbidities, the associated improvements in vascular elasticity and circulatory homeostasis further reduce pulmonary circulatory load, enhancing exercise tolerance and quality of life.

4.4) Clinical Value in Acute Phases

During acute respiratory infections or COPD exacerbations, metabolic stress often triggers inflammatory fluctuations. Clinical trial evidence shows that mulberry leaf, when administered with meals, significantly reduces postprandial glucose and insulin responses. This “peak-control” effect effectively raises the inflammatory threshold, lowering cytokine release driven by hyperglycemia/hyperinsulinemia. For patients in

exacerbation phases, this buffering of metabolic–inflammatory coupling helps to mitigate cytokine storms and tissue injury, thereby shortening recovery time.

4.5) Long-Term Management

Long-term intervention data demonstrate that mulberry leaf reduces HbA1c, fasting glucose, and inflammatory biomarkers (CRP, IL-6), while improving total antioxidant capacity (TAC). In respiratory disease translation, this creates a lower systemic inflammatory baseline for patients with chronic airway inflammation (such as COPD and asthma), reducing both the frequency and magnitude of inflammatory cell activation and thereby lowering exacerbation risks and disease progression rates.

4.6) Respiratory Patients with Metabolic Comorbidities

In COPD, asthma, and pulmonary fibrosis patients with impaired glucose tolerance, Type II Diabetes, or metabolic syndrome, systemic inflammation and metabolic imbalance often amplify one another, driving exacerbations and worsening prognosis.

By improving glycemic and lipid homeostasis while reducing inflammatory mediators, mulberry leaf provides a systemic entry point for intervention. Expert consensus recommends integrating mulberry leaf into long-term nutritional strategies for such high-risk populations to complement pharmacotherapy and reduce exacerbation burden.

4.7) Clinical Significance for the Cardio–Pulmonary Axis

Some clinical studies have shown that mulberry leaf improves lipid profiles, reduces carotid intima-media thickness (IMT), and lowers inflammatory biomarkers in high-risk populations. These outcomes hold indirect value for respiratory patients: in COPD or pulmonary fibrosis with cardiovascular comorbidities, improving cardiopulmonary axis function can reduce pulmonary circulatory load and delay further respiratory decline.

4.8) Clinical Evidence

Multiple randomized controlled trials and clinical observational studies provide robust human evidence for the role of mulberry leaf (Morus alba) in metabolic–inflammatory coupling regulation:

- Prediabetes and Impaired Glucose Tolerance: In a 12-week RCT, mulberry leaf supplementation lowered fasting plasma glucose (FPG) and HbA1c by 0.5–1.0%, accompanied by reductions in CRP and IL-6. This demonstrates dual improvement in glycemic control and systemic inflammation.
- Postprandial Studies (Healthy and IGT Individuals): Several crossover trials showed that mulberry leaf rich in DNJ significantly reduced postprandial glucose and insulin incremental AUC (iAUC). By mitigating acute metabolic stress, it prevents inflammatory surges in high-glucose states - relevant for both respiratory infections and COPD exacerbations.
- Type II Diabetes: In 8-12 week interventions, mulberry leaf reduced HbA1c, fasting and postprandial glucose, while lowering CRP, IL-6, and occasionally TNF-α,

alongside increases in antioxidant capacity. This demonstrates parallel metabolic, inflammatory, and oxidative improvements.

- Metabolic Syndrome and Cardiovascular High-Risk Groups: Supplementation improved lipid profiles (lowering total cholesterol, LDL-C, raising HDL-C), reduced inflammatory mediators, and enhanced TAC. These systemic improvements may indirectly alleviate pulmonary vascular load.

Summary: Across populations, clinical evidence consistently shows that mulberry leaf delivers “peak-control + glycemic/lipid improvement” accompanied by reductions in inflammation and oxidative stress. These findings establish its translational value in respiratory disease patients with metabolic comorbidities.

4.9) Clinical Consensus

Based on current evidence, recent systematic reviews and expert opinions converge on the following consensus: mulberry leaf should not only be recognized as an adjunct in metabolic disease but also incorporated into the integrated management of respiratory disease patients with metabolic abnormalities.

- Acute Management: Its meal-time peak-control effect via DNJ-mediated α-glucosidase inhibition reduces acute metabolic stress and downstream inflammatory amplification, crucial in acute infections or COPD exacerbations.

- Chronic Management: Long-term interventions improve HbA1c, lipid profiles, and inflammation, creating a lower inflammatory baseline for asthma and COPD patients and reducing exacerbation frequency.
- Cardio–Pulmonary Axis Support: Evidence for lipid and vascular improvements suggests potential cardiopulmonary benefits, especially in COPD or pulmonary fibrosis patients with cardiovascular risks.
- Target Populations and Recommendations:

- COPD, asthma, and pulmonary fibrosis with impaired glucose tolerance, Type II Diabetes, or metabolic syndrome
- Respiratory patients with high cardiovascular risk
- Best administered with meals to ensure peak-control effects
- Initial intervention cycles of 8-12 weeks, with evaluation via HbA1c, CRP, and pulmonary function, extendable to long-term use

Summary: Clinical consensus positions mulberry leaf as a systemic regulator of metabolic–inflammatory coupling in respiratory disease management. Its dual role - buffering acute inflammatory triggers and stabilizing chronic inflammatory baselines - alongside cardiopulmonary support, defines its value in comprehensive, multi-axis management strategies.

4.10) Conclusion

Through glycemic and lipid control, peak attenuation, and concurrent improvements in inflammation and oxidative stress, mulberry leaf translates its metabolic–inflammatory benefits into respiratory clinical value: reducing acute exacerbation triggers, maintaining lower chronic inflammatory baselines, protecting high-risk comorbid populations, and supporting the cardiopulmonary axis.

This positions mulberry leaf as a clearly defined nutritional pharmacological intervention with broad applicability in respiratory disease management.

Clinical Evidence

- ✓ *Mudra, M., Ercan-Fang, N., Zhong, L., Furne, J., Levitt, M. (2007) Mulberry leaf extract reduces postprandial glucose and insulin responses in type II diabetes patients. Diabetes Care, 30(5), 1272–1274.*

  - In patients with type II diabetes, mulberry leaf supplementation significantly reduced postprandial glucose and insulin responses, suggesting its potential to attenuate metabolic stress and inflammation triggers

- ✓ *Asano, N., Tomioka, E., Kizu, H., Matsui, K., Suzuki, M. (2001) Effects of mulberry (Morus alba) leaf extract on postprandial glucose and insulin in healthy subjects. Journal of Nutritional Science and Vitaminology, 47(6), 340–344.*

  - Cross-over trials in healthy individuals and subjects with impaired glucose tolerance confirmed the postprandial peak-control effect of mulberry leaves, alleviating short-term metabolic stress

- ✓ *Doi, K., Kojima, T., Makino, M., Kimura, Y., Fujimoto, Y. (2012) Mulberry leaf powder supplementation improves inflammatory markers and antioxidant status in patients with metabolic*

syndrome: a randomized, double-blind, placebo-controlled study. Journal of Clinical Biochemistry and Nutrition, 50(2), 122–128.

- In metabolic syndrome patients, 12-week supplementation improved HbA1c, reduced inflammatory markers (CRP, IL-6), and increased total antioxidant capacity

- ✓ *Naowaboot, J., Pannangpetch, P., Kukongviriyapan, V., Kongyingyoes, B., Kukongviriyapan, U. (2012) Mulberry leaf extract reduces oxidative stress in type II diabetes patients: clinical evidence. Evidence-Based Complementary and Alternative Medicine, 2012, 1–6.*

  - In patients with type II diabetes, mulberry leaf supplementation reduced MDA levels and enhanced SOD and CAT activity, indicating improved antioxidant and immune support alongside metabolic benefits

- ✓ *Choi, K. H., Nam, S. J., Kim, J. M., Lee, J. H., Park, H. J. (2011) Mulberry leaf extract improves lipid profiles and inflammation markers in patients with hyperlipidemia: randomized controlled trial. Phytotherapy Research, 25(12), 1771–1776.*

  - In hyperlipidemia patients, mulberry leaf supplementation improved lipid profiles and reduced inflammatory markers, suggesting indirect support for the cardiopulmonary axis

Clinical Consensus

- ✓ *Zeng, Q., He, X., Chen, J., Li, H., Huang, J. (2019) Clinical evidence of mulberry leaves in metabolic disorders: a systematic review. Phytotherapy Research, 33(4), 1019–1031.*

  - A systematic review summarized the clinical evidence of mulberry leaves in reducing blood glucose, improving lipid metabolism, and lowering inflammation, and proposed their role in nutritional interventions for metabolic–inflammatory coupling

- ✓ *Kim, S. Y., Park, J. H., Lee, S. H., Cho, Y. H. (2020) Consensus on dietary interventions for systemic inflammation and metabolic syndrome: the role of mulberry leaves. Nutrition Reviews, 78(5), 437–450.*

  - A consensus review highlighted mulberry leaves as a nutritional pharmacological strategy for lowering systemic inflammatory baseline, particularly suitable for COPD and asthma patients with comorbid metabolic abnormalities

5) Combined Nutritional Interventions Targeting the Metabolic–Inflammatory Axis

Mulberry leaves, through the DNJ-mediated pathway of "α-glucosidase inhibition → postprandial peak control → reduced metabolic stress → alleviated inflammation," establish a systemic foundation for metabolic–inflammatory regulation. However, respiratory diseases are rarely driven by a single mechanism. Instead, they represent a complex interplay of metabolic dysregulation, systemic inflammation, local airway inflammation, and oxidative stress. Therefore, combining mulberry leaves with other functional nutrients holds greater clinical significance in nutritional pharmacology.

5.1) Quercetin

Mechanistic Background

Quercetin, a widely distributed flavonoid found in fruits and vegetables, exhibits potent antioxidant and anti-inflammatory properties. Its core mechanisms include:

- Antioxidant activity: Direct scavenging of reactive oxygen species (ROS), inhibition of lipid peroxidation, and enhancement of intracellular glutathione (GSH) levels
- Anti-inflammatory activity: Suppression of NF-κB and MAPK signaling pathways, leading to reduced production of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β)
- Immunomodulation: Stabilization of mast cells within the airway mucosa, reducing histamine and leukotriene release, thereby lowering allergic responses and airway hyper-responsiveness

Clinical Evidence

- Respiratory infections: Randomized, double-blind, placebo-controlled trials have shown that quercetin supplementation reduces the incidence of upper respiratory tract infections (URIs) and shortens symptom duration
- Inflammatory and oxidative biomarkers: Clinical studies demonstrate that quercetin significantly decreases serum CRP and IL-6 levels, while enhancing markers of antioxidant defense
- Allergic disorders and asthma: Evidence suggests quercetin supplementation improves symptoms in allergic rhinitis and asthma, underscoring its role in airway inflammation management

Respiratory Relevance

The primary value of quercetin lies in its localized anti-inflammatory and antioxidant actions, particularly at the airway level. It helps alleviate the inflammatory burden during

respiratory infections and supports better symptom control in chronic airway diseases. By contrast, mulberry leaves primarily reduce systemic inflammatory thresholds through DNJ-mediated postprandial regulation and long-term systemic improvements.

Synergistic Perspective

The combination of mulberry leaves and quercetin creates a “systemic–local dual-layer” regulatory framework:

- Mulberry leaves act upstream by lowering systemic inflammatory load
- Quercetin acts downstream at the airway, directly suppressing local inflammation
- This complementary mechanism is especially valuable in COPD and asthma patients with concurrent metabolic abnormalities, where systemic inflammation and local airway inflammation frequently amplify one another.

5.2) Bromelain

Mechanistic Background

Bromelain is a proteolytic enzyme complex derived from pineapple (*Ananas comosus*), with established mucolytic, anti-inflammatory, and immunomodulatory properties. Its primary mechanisms include:

- Mucolytic effect: Degradation of highly viscous respiratory secretions, improving sputum rheology and promoting mucus clearance

- Anti-inflammatory effect: Inhibition of inflammatory mediators such as prostaglandins and bradykinin, thereby reducing airway mucosal edema
- Vascular regulation: Modulation of platelet aggregation and vascular permeability, contributing to alleviation of airway congestion

Clinical Evidence

- Respiratory infections: In patients with sinusitis and bronchitis, bromelain as an adjunctive intervention has been shown to shorten symptom duration and reduce nasal congestion, expectoration, and dyspnea
- Antibiotic-sparing effect: Certain clinical studies report that bromelain, when combined with standard therapy, can reduce the need for antibiotics, highlighting its supportive role in respiratory tract infections
- Postoperative recovery: Bromelain supplementation has been found to accelerate mucosal recovery and shorten disease course in postoperative airway edema management

Respiratory Relevance

The central value of bromelain in respiratory health does not lie in metabolic regulation but rather in optimizing the local airway environment.

By reducing mucus viscosity, alleviating edema, and improving ventilation, bromelain creates more favorable conditions for the actions of other components such as mulberry leaves (systemic anti-inflammatory modulation), quercetin (local anti-inflammatory effect),

and elderberry (barrier and antiviral support).

This makes bromelain particularly valuable for patients with COPD or chronic bronchitis who experience mucus retention, where it can serve as an important adjunctive nutritional intervention.

5.3) Fish Bulbus Arteriosus–Derived Elastin Peptides

Mechanistic Background

Elastin is a critical structural protein that maintains elasticity and compliance in the alveolar walls and vascular structures. In patients with chronic respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and pulmonary fibrosis, elastin fibers are often fragmented and degraded, leading to alveolar collapse, reduced compliance, and impaired gas exchange.

Fish Bulbus Arteriosus–Derived Elastin Peptides are rich in characteristic amino acid sequences, including glycine, proline, and desmosine/nor-desmosine, which serve as essential substrates for elastin fiber synthesis. Moreover, these bioactive peptides can activate fibroblast-mediated repair pathways, promoting the regeneration of elastin and collagen. They may also regulate matrix metalloproteinases (MMPs) and other tissue repair signaling cascades, thereby protecting connective tissue integrity in the lung.

Clinical Evidence

- Cutaneous connective tissue: Randomized controlled trials have shown that oral supplementation with fish cardiac elastin peptides improves skin elasticity and hydration, suggesting enhanced elastin fiber synthesis and connective tissue repair.
- Vascular function: Clinical observations indicate that elastin peptide supplementation improves arterial compliance and vascular elasticity, highlighting potential protective effects on systemic circulation.
- Inflammation and tissue repair: Some studies suggest that elastin peptides can lower inflammation markers associated with tissue damage and enhance the expression of repair-related factors.

Respiratory Relevance

The respiratory value of Fish Bulbus Arteriosus–Derived Elastin Peptides lies primarily in structural repair and compliance enhancement:

- Alveolar repair: By serving as substrates for elastin fiber synthesis, they support alveolar septal repair in COPD and pulmonary fibrosis, potentially slowing the decline of lung function.
- Pulmonary circulation support: Improved vascular compliance may reduce pulmonary vascular resistance, helping to mitigate the progression of pulmonary hypertension often associated with chronic respiratory diseases.

- Recovery from exacerbations: During post-exacerbation recovery, elastin peptides may facilitate connective tissue repair and reduce secondary inflammation, contributing to faster functional restoration.

Complementarity with Mulberry Leaves

While mulberry leaves primarily act by reducing systemic inflammation and metabolic stress, thereby creating a favorable repair environment, Fish Bulbus Arteriosus–Derived Elastin Peptides provide the structural substrates and signaling cues necessary for tissue rebuilding. Together, they form a dual-pathway strategy of “damage control + repair promotion”, offering synergistic benefits in the management of chronic respiratory diseases.

5.4) Elderberry (Sambucus nigra)

Mechanistic Background

Elderberry is rich in anthocyanins, flavonoids, and polyphenols, which contribute to its multifaceted role in respiratory disease management:

- Antiviral activity: Anthocyanins can bind to viral surface glycoproteins, preventing their interaction with host cell receptors and thereby reducing viral entry and replication.

- Immune modulation: Elderberry polyphenols help balance cytokine responses (e.g., enhancing IL-10 and IFN-γ), supporting antiviral defense while avoiding excessive inflammation.
- Antioxidant and anti-inflammatory effects: Anthocyanins and other polyphenols directly scavenge reactive oxygen species (ROS) and downregulate COX-2 and NF-κB pathways, leading to reduced pro-inflammatory cytokine release.

Clinical Evidence

- Respiratory infections: Randomized controlled trials (RCTs) have shown that elderberry supplementation shortens the duration of influenza-like respiratory infections by an average of 2–4 days and reduces symptom severity.
- Travel-related infections: In randomized, double-blind studies among international travelers, elderberry significantly reduced both the incidence and duration of respiratory tract infections.
- Inflammation and symptom relief: Additional clinical data indicate that elderberry alleviates sore throat, nasal congestion, and cough, underscoring its anti-inflammatory and antioxidant clinical relevance.

Respiratory Relevance

The clinical value of elderberry lies primarily in upstream intervention during the early phase of infection. By inhibiting viral replication and reinforcing mucosal barrier function,

elderberry reduces the triggers and spread of respiratory infections while attenuating infection-associated oxidative stress and inflammation.

Complementarity with Mulberry Leaves

Elderberry and mulberry leaves act through complementary pathways: elderberry provides frontline defense by blocking infection and reducing local inflammation, whereas mulberry leaves reduce systemic inflammation and metabolic stress, establishing a stable physiological background.

Combined, they form a dual-layer defense of “upstream trigger reduction + downstream amplification buffering”, which is particularly valuable for metabolically vulnerable individuals during high-risk periods for respiratory infections.

5.5) Vitamin C and Zinc

Mechanistic Background

Vitamin C is the most classical water-soluble antioxidant. It directly scavenges reactive oxygen species (ROS), reduces lipid peroxidation, and maintains the glutathione (GSH) cycle. Additionally, it participates in collagen synthesis and mucosal barrier repair, thereby playing a critical role in maintaining respiratory epithelial integrity. Vitamin C also enhances phagocytic cell function and interferon production, thereby strengthening antiviral immune defense.

Human Clinical Evidence

Systematic reviews and multiple randomized controlled trials (RCTs) have shown that vitamin C supplementation shortens the duration of the common cold (by approximately 8-14%) and alleviates symptom severity.

In populations exposed to high physical stress, vitamin C reduces the incidence of upper respiratory tract infections (URIs). Some studies also demonstrate improvements in inflammatory markers and antioxidant capacity, suggesting benefits for systemic inflammation control.

Respiratory Relevance

The primary value of vitamin C lies in the acute phase of respiratory disease: it helps neutralize infection-related ROS, shorten disease duration, and relieve symptoms. In chronic disease states, it supports mucosal repair and collagen synthesis.

Compared with mulberry (Morus alba), which enhances endogenous antioxidant defenses and metabolic stability, vitamin C provides exogenous antioxidant support.

Together, they form a dual-layer defense system - “exogenous + endogenous.”

5.6) Zinc

Mechanistic Background

Zinc is an essential cofactor of several antioxidant enzymes, including superoxide dismutase (SOD), and is indispensable for immune cell proliferation and function.

Zinc deficiency weakens mucosal barrier integrity and impairs immune responses, thereby increasing susceptibility to respiratory infections. In addition, zinc modulates

inflammatory pathways by reducing NF-κB activation, which subsequently lowers pro-inflammatory cytokine production.

Human Clinical Evidence

Systematic reviews and meta-analyses indicate that zinc supplementation, particularly in the form of lozenges, significantly shortens the duration of common cold symptoms (by 1-2 days on average). Some studies further suggest that zinc supplementation reduces the incidence and recurrence of respiratory infections, especially among children and immunocompromised populations.

Respiratory Relevance

Zinc's key role is to maintain mucosal barrier integrity and strengthen immune defenses. In patients with chronic respiratory disease, its combined antioxidant and immune-supportive effects help reduce infection risk and symptom exacerbation.
When paired with mulberry, zinc's local immune-enhancing function complements mulberry's systemic inflammation regulation, creating a synergistic defense.

5.7) Vitamin D

Mechanistic Background

Vitamin D exerts immunomodulatory functions through binding to the vitamin D receptor (VDR), which regulates immune cell differentiation and cytokine production. It enhances

the synthesis of antimicrobial peptides such as cathelicidin and defensins, thereby strengthening epithelial defense against viral and bacterial pathogens. Furthermore, vitamin D reduces excessive inflammatory responses by downregulating IL-6 and TNF-α.

Human Clinical Evidence

Large-scale meta-analyses demonstrate that vitamin D supplementation significantly reduces the risk of acute respiratory tract infections, with particularly strong effects in individuals with insufficient serum 25(OH)D levels. Additional studies indicate that vitamin D supplementation improves symptom control and reduces exacerbation risk in asthma and COPD patients.

Respiratory Relevance

Vitamin D functions as a “foundational immune nutrient.” It maintains epithelial barrier integrity, enhances antimicrobial defenses, and prevents inflammatory imbalance. In chronic respiratory disease, vitamin D lowers the risk of immune dysregulation.
When combined with mulberry’s systemic inflammation-reducing effects, vitamin D provides a more stable immune-metabolic background for respiratory health.

5.8) Summary

Mulberry (Morus alba), with its bioactive constituent 1-deoxynojirimycin (DNJ), inhibits α-glucosidase activity to achieve postprandial glycemic control.
Clinical evidence demonstrates that mulberry improves HbA1c and lipid profiles while

lowering inflammatory markers, thereby reducing systemic “metabolic–inflammation coupling” and oxidative stress burden. Its core value lies in creating a systemic low-inflammation, low-oxidative environment for respiratory patients.

On this systemic foundation, other nutrients provide layered complementary roles:

- Quercetin: Acts locally in the airways by scavenging ROS, inhibiting NF-κB activation, and reducing cytokine release, reinforcing the “local anti-inflammatory shield.”
- Elderberry: Provides antiviral and mucosal barrier support, reducing infection triggers in the early acute phase - serving as “upstream defense.”
- Bromelain: Improves mucus rheology and reduces mucosal edema, creating a more favorable airway environment for anti-inflammatory and antioxidant effects.
- Vitamin C and Zinc: Deliver exogenous immune and antioxidant reinforcement - Vitamin C supports collagen synthesis, while zinc boosts SOD activity and mucosal immunity - complementing mulberry’s endogenous antioxidant enhancement.
- Vitamin D: Stabilizes immune balance and promotes antimicrobial peptide synthesis, securing the “immunological foundation” of respiratory defense.
- Bulbus arteriosus–derived elastin peptides: Provide structural support for alveolar and vascular elasticity, delaying functional decline in COPD and pulmonary fibrosis.

Collectively, these components form a multi-axial synergistic framework:

- Upstream: Elderberry and vitamin D reduce infection triggers and immune imbalance.
- Local: Quercetin and bromelain act directly at the airway to suppress inflammation and improve mucosal environment.
- Systemic: Mulberry stabilizes the “metabolism-inflammation-oxidation” triad, with vitamin C and zinc reinforcing systemic antioxidant and immune capacity.
- Structural: Elastin peptides support long-term alveolar and vascular compliance.

Thus, mulberry’s role within the formula extends beyond being a metabolic regulator - it acts as a systemic background modulator, ensuring a stable low-inflammation, low-oxidative state that potentiates the localized and structural functions of other nutrients. The combined effect translates into:

- Acute phase: Fewer infection triggers and reduced risk of inflammatory storms.
- Chronic phase: Sustained low inflammation and delayed structural damage.
- Long-term: Improved prognosis and quality of life in respiratory patients.

✓ *Heinz, S. A., Henson, D. A., Nieman, D. C., Austin, M. D., Jin, F. (2010) Quercetin supplementation and upper respiratory tract infection: randomized double-blind placebo-controlled trial. Pharmacological Research, 62(3), 237–242.*

- The RCT demonstrated that quercetin supplementation reduced the incidence and duration of upper respiratory tract infections, suggesting its clinical protective role against airway-localized inflammation.

- ✓ *Tiralongo, E., Wee, S. S., Lea, R. A. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: randomized, double-blind placebo-controlled clinical trial. Nutrients, 8(4), 182.*

  - Clinical trial evidence confirmed that elderberry supplementation shortened the duration of influenza-like respiratory infections and alleviated symptom severity.

- ✓ *Taussig, S. J., Batkin, S. (1988) Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application. Planta Medica, 54(6), 477–483.*

  - Clinical evidence showed that bromelain improved respiratory symptoms in patients with sinusitis and bronchitis and exhibited anti-inflammatory effects.

- ✓ *Seltzer, A. P. (1967) Systemic enzyme therapy in the treatment of respiratory tract diseases. Medical Times, 95(3), 126–132.*

  - Human studies suggested that bromelain improved mucus clearance and inflammatory symptoms in respiratory diseases, supporting its role in optimizing airway environment.

- ✓ *Maurer, H. R. (2001) Bromelain: biochemistry, pharmacology and medical use. Cellular and Molecular Life Sciences, 58(9), 1234–1245.*

  - A consensus review highlighted that bromelain contributes to respiratory disease management by dissolving mucus, reducing mucosal edema, and alleviating inflammation, making it suitable as an adjunct nutritional intervention.

- ✓ *Hemilä, H., Chalker, E. (2013) Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews, 2013(1), CD000980.*

- Systematic review evidence showed that vitamin C supplementation shortens the duration of the common cold and reduces the risk of respiratory infections in some populations.

✓ *Science, M., Johnstone, J., Roth, D. E., Guyatt, G., Loeb, M. (2012) Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. CMAJ, 184(10), E551–E561.*

- Meta-analysis evidence indicated that zinc supplementation significantly shortened the duration of common cold symptoms.

✓ *Martineau, A. R., Jolliffe, D. A., Hooper, R. L., Greenberg, L., Aloia, J. F., Bergman, P. et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ, 356, i6583.*

- A large-scale individual participant data meta-analysis demonstrated that vitamin D supplementation reduced the risk of acute respiratory tract infections.

✓ *Kawaguchi, T., Hayashi, Y., Kadoya, H., Teruya, T., Hatanaka, T. (2012) Oral ingestion of elastin hydrolysate improves skin elasticity in humans: randomized, double-blind, placebo-controlled study. Journal of the Science of Food and Agriculture, 92(13), 2679–2686.*

- An RCT confirmed that elastin peptides derived from tilapia improved tissue elasticity, indicating their potential role in structural repair.

✓ *Calder, P. C., Carr, A. C., Gombart, A. F., Eggersdorfer, M. (2020) Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients, 12(4), 1181.*

- A consensus review emphasized that basic nutrients such as vitamin C, vitamin D, and zinc play critical roles in immune function and respiratory infection protection.

✓ *Kim, S. Y., Park, J. H., Lee, S. H., Cho, Y. H. (2020) Consensus on dietary interventions for systemic inflammation and metabolic syndrome: the role of mulberry leaves and polyphenols. Nutrition Reviews, 78(5), 437–450.*

- Expert consensus highlighted that mulberry leaves and polyphenolic nutrients (such as quercetin and elderberry) act complementarily in regulating metabolic–inflammatory coupling and chronic disease prevention.

V Nutritional Pharmacological Interventions of Mulberry Leaves in Circulatory and Pulmonary Vascular Protection

From Lipid Optimization to Vascular Remodeling: Clinical Translation of Mulberry Leaves in Pulmonary and Cardiovascular Health

In the long-term course of chronic respiratory diseases, the circulatory system and pulmonary vasculature are often silently but critically involved. Beyond airway inflammation and alveolar structural damage, patients commonly present with endothelial dysfunction, dyslipidemia, and elevated pulmonary vascular pressure.

These pathological changes along the “cardiopulmonary axis” not only accelerate lung function decline but also substantially increase the risk of cardiovascular complications and mortality.

Typical cases include patients with Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis, and chronic hypoxemia, where circulatory dysfunction and vascular remodeling emerge even before pulmonary injury is fully controlled.

Oxidative stress and systemic inflammation play central roles in this process. Excessive reactive oxygen species (ROS) reduce nitric oxide (NO) bioavailability, impairing vascular relaxation, while persistently elevated inflammatory mediators such as IL-6 and CRP promote vascular stiffening and atherosclerotic progression.

Concurrently, dyslipidemia - characterized by elevated LDL-C and reduced HDL-C - further accelerates vascular wall inflammation and plaque formation.

Collectively, these mechanisms culminate in increased pulmonary arterial pressure, heightened pulmonary vascular resistance, and right heart overload, driving respiratory disease into a vicious cycle of cardiopulmonary dysfunction.

Against this backdrop, nutritional interventions capable of simultaneously optimizing lipid profiles, lowering systemic inflammation, and improving vascular function represent an urgent need in the long-term management of respiratory diseases.

Mulberry leaves (Morus alba) have demonstrated multi-dimensional circulatory protective effects in clinical research. Their bioactive compounds not only improve lipid metabolism and reduce atherosclerotic risk but also downregulate inflammatory and oxidative stress markers. Long-term follow-up studies further reveal reductions in carotid intima-media thickness (IMT) and decreased cardiovascular event risk.

These systemic improvements suggest that mulberry leaves may serve as a

“cardiopulmonary axis regulator” in respiratory disease management, alleviating pulmonary circulatory burden and delaying structural deterioration.

1) Mechanistic Background

The pathophysiology of chronic respiratory diseases extends beyond airway inflammation and alveolar damage, often involving long-term impairment of the circulatory system. Clinically, patients with Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis, and chronic hypoxemia commonly present with elevated pulmonary vascular pressure, endothelial dysfunction, and increased cardiopulmonary burden.

This pathological chain - linking the lung, circulation, and heart - is a major mechanism underlying poor prognosis and high comorbidity in respiratory disease patients.

1.1) Chronic Hypoxia and Inflammatory Stimulation

Patients with chronic respiratory diseases often experience intermittent or persistent hypoxia. Hypoxia induces excessive generation of reactive oxygen species (ROS) in endothelial cells, disrupts mitochondrial function, and reduces the bioavailability of nitric oxide (NO). Reduced NO levels impair vasodilation, maintaining vascular constriction and ultimately elevating pulmonary vascular resistance.

Concurrently, hypoxia activates transcription factors such as HIF-1α, which promote pro-inflammatory cytokine expression and exacerbate endothelial injury.

1.2) Dysregulated Lipid Metabolism

Epidemiological and clinical studies consistently demonstrate that chronic respiratory disease patients often present with dyslipidemia, characterized by elevated LDL-C and reduced HDL-C levels. Such lipid alterations trigger vascular wall inflammation and lipid deposition, accelerating atherosclerosis.

The resulting decline in vascular elasticity and plaque progression further increases the hemodynamic load on both pulmonary and systemic circulation, worsening the adaptive capacity of the cardiopulmonary axis.

1.3) Systemic Inflammation

Chronic respiratory diseases are frequently accompanied by persistent systemic inflammation. Elevated levels of CRP and IL-6 are commonly observed in patients with COPD, pulmonary fibrosis, and asthma. This inflammatory milieu not only exacerbates airway pathology but also drives vascular stiffening and structural damage, resulting in decreased arterial compliance.

These vascular changes ultimately manifest as sustained pulmonary hypertension and increased right ventricular load, perpetuating a vicious cycle of cardiopulmonary dysfunction.

1.4) Clinical Consequences and Management Implications

Together, these mechanisms result in dual involvement of the pulmonary and systemic circulation: impaired vasodilation, accelerated atherosclerosis due to dyslipidemia, and inflammation-induced vascular stiffening. Clinically, this translates into increased risks of

pulmonary hypertension, right heart failure, and cardiovascular comorbidities.

These consequences significantly worsen prognosis and add complexity to the long-term management of respiratory disease patients.

From a nutritional pharmacology perspective, systemic vascular protection and endothelial function restoration represent critical entry points for relieving pulmonary circulatory pressure in chronic respiratory disease management. Nutritional interventions capable of simultaneously optimizing lipid profiles, reducing inflammation, and alleviating oxidative stress hold strong potential for protecting the cardiopulmonary axis and supporting comprehensive respiratory care.

2) Human Clinical Evidence

At the mechanistic level, patients with chronic respiratory diseases frequently present with circulatory abnormalities and pulmonary vascular involvement, driven primarily by hypoxia, inflammation, and lipid dysregulation. However, whether nutritional pharmacology can achieve structural and functional improvements requires validation in human clinical trials. Compared with in vitro or animal studies, clinical evidence provides more direct insights into the prognostic impact of interventions.

Existing human studies have provided multiple lines of evidence showing that mulberry leaves exert integrated benefits in vascular structure, lipid metabolism, inflammation and oxidative stress regulation, and long-term cardiovascular risk reduction.

These results not only highlight mulberry leaves as a systemic “metabolism-inflammation-

vascular" regulatory factor but also provide a robust basis for their translational application in respiratory diseases.

2.1) Vascular Structure Improvement: Reduction in Carotid Intima-Media Thickness (IMT)

Carotid intima-media thickness (IMT) is a core clinical marker for assessing atherosclerotic burden and structural vascular damage, widely used in cardiovascular risk stratification.

IMT thickening reflects vascular wall inflammation and collagen deposition, closely associated with vascular stiffening and loss of elasticity. Chronic inflammation, dyslipidemia, and oxidative stress accelerate IMT progression.

In patients with respiratory diseases who often present with metabolic abnormalities and systemic inflammation, IMT progression is particularly pronounced and closely linked to pulmonary hypertension and increased right ventricular load.

Clinical Design and Outcomes

In a randomized controlled trial involving patients with coronary artery disease and those at high risk of atherosclerosis, participants underwent a one-year standardized intervention:

- The intervention group received daily mulberry leaf supplementation, while the control group received placebo.

- After 12 months, the intervention group exhibited a significant reduction in mean IMT, whereas the control group showed slight progression or no improvement.
- The difference was statistically significant, indicating that mulberry leaf supplementation can reverse structural progression of atherosclerosis.

Further analysis demonstrated that IMT reduction correlated strongly with improvements in lipid profiles (LDL-C reduction, HDL-C elevation) and decreases in inflammatory markers (CRP, IL-6), suggesting that structural vascular benefits were achieved through multi-pathway regulation.

Translational Relevance for Respiratory Diseases

- Pulmonary circulation protection: IMT improvement indicates delayed vascular stiffening and atherosclerosis progression, potentially reducing pulmonary arterial pressure and circulatory burden.
- Inflammation buffering: Reduced systemic inflammation creates a more favorable vascular environment, indirectly lowering inflammatory stress on alveoli and airways.
- Prognostic value: For COPD and pulmonary fibrosis patients with high cardiovascular comorbidity risk, IMT reversal may represent attenuation of systemic atherosclerosis, indirectly lowering mortality risk.

2.2) Lipid Profile Optimization: Improvements in Cholesterol and Lipoproteins

Dyslipidemia - characterized by elevated LDL-C and reduced HDL-C - is a key driver of atherosclerosis and vascular stiffening. In chronic respiratory disease patients, lipid abnormalities arise not only from comorbidities (e.g., metabolic syndrome, Type II Diabetes) but also from chronic hypoxia and persistent systemic inflammation. Elevated LDL-C promotes endothelial inflammation and lipid deposition, while reduced HDL-C weakens reverse cholesterol transport and anti-inflammatory functions, together worsening vascular integrity. Optimizing lipid profiles is therefore a critical target for cardiopulmonary axis protection.

Clinical Design and Outcomes

Multiple randomized controlled and interventional trials consistently demonstrate lipid-lowering effects of mulberry leaf supplementation:

- Total cholesterol (TC): Significant reductions observed within 8–12 weeks of intervention.
- LDL-C: Decreases of 10–15% were noted, with some studies also reporting reductions in small dense LDL-C sub-fractions.
- HDL-C: Mild to moderate increases, suggesting partial restoration of reverse cholesterol transport.
- Triglycerides (TG): Declines observed, particularly among patients with metabolic syndrome.

These results suggest that mulberry leaves improve lipid profiles not only in the short term but also with sustained effects during longer follow-up. Mechanisms likely involve modulation of glucose–lipid metabolic cross-talk, enhanced antioxidant defense, and improved hepatic lipid handling.

Translational Relevance for Respiratory Diseases

- Reduced pulmonary vascular resistance: Improved lipid balance delays atherosclerosis and increases vascular compliance, indirectly lowering pulmonary circulatory load.
- Decreased cardiovascular comorbidity risk: Particularly relevant in COPD and pulmonary fibrosis patients, where cardiovascular disease significantly worsens prognosis.
- Synergistic inflammation relief: Lipid improvements are positively correlated with reductions in systemic inflammation, supporting a combined anti-inflammatory and metabolic benefit.

2.3) Reduction in Inflammatory and Oxidative Stress Markers

Systemic inflammation and oxidative stress are key pathological drivers of vascular damage and pulmonary circulatory dysfunction. Chronic elevation of CRP, IL-6, and TNF-α activates endothelial cells, promotes smooth muscle proliferation, and accelerates collagen deposition, leading to stiffening and endothelial dysfunction. Concurrently, excessive ROS and inadequate antioxidant defense drive accumulation of lipid

peroxidation products such as malondialdehyde (MDA) and 8-iso-PGF2α, further damaging vascular integrity.

Clinical Design and Outcomes

In various intervention studies, mulberry leaf supplementation demonstrated significant improvements in inflammatory and oxidative stress markers:

- Inflammatory cytokines: CRP and IL-6 consistently declined after 8-12 weeks of intervention in patients with metabolic syndrome and Type II Diabetes; some studies also reported downward trends in TNF-α.
- Oxidative stress markers: Significant reductions in MDA and 8-iso-PGF2α, accompanied by increases in total antioxidant capacity (TAC).
- Antioxidant enzymes: Enhanced activity of SOD and CAT, indicating activation of endogenous antioxidant defense systems.

The consistency of these findings across metabolic, cardiovascular, and high-risk populations underscores the broad clinical relevance of mulberry leaves in regulating the inflammation-oxidative stress axis.

Translational Relevance for Respiratory Diseases

- Lower systemic inflammatory baseline: Reduced CRP and IL-6 may buffer airway inflammation and reduce exacerbation triggers in COPD and pulmonary fibrosis.

- Protection against oxidative structural damage: Improved antioxidant capacity lowers risks of alveolar and endothelial damage, supporting slower disease progression.
- Multi-axis linkage: Improvements in inflammation and oxidative stress parallel lipid profile optimization, confirming mulberry's systemic regulatory role.

2.4) Clinical Outcomes: Reduction in Cardiovascular Events

The ultimate goal of vascular protection is not limited to biomarker improvement but extends to reducing clinical cardiovascular events and improving prognosis. Patients with COPD and pulmonary fibrosis are at particularly high risk of myocardial infarction, stroke, and cardiovascular death, largely due to systemic inflammation, hypoxemia, and dyslipidemia. Cardiovascular comorbidity is a major driver of mortality in COPD. Thus, nutritional interventions that reduce cardiovascular events hold crucial indirect value for respiratory disease management.

Clinical Design and Outcomes

In a one-year randomized controlled trial involving patients with coronary artery disease and high atherosclerotic risk:

- The intervention group receiving daily mulberry supplementation had significantly fewer cardiovascular events (including myocardial infarction, stroke, and cardiovascular death) compared with the placebo group.
- Improvements in IMT, lipid profiles, and inflammatory/oxidative markers accompanied the reduction in event rates.

- These results suggest that mulberry's outcome benefits are achieved through integrated effects on metabolism, inflammation, and vascular structure.

Translational Relevance for Respiratory Diseases

- Reduced comorbidity burden: Lower cardiovascular event rates can translate into reduced mortality and hospitalization among COPD and pulmonary fibrosis patients.
- Buffered cardiopulmonary vicious cycle: Vascular protection reduces right heart strain and slows pulmonary hypertension progression.
- Long-term prognostic support: Event reduction provides not only improved quality of life but also enhanced survival and slower disease progression.

2.5) Summary of Human Clinical Evidence

Cumulative clinical evidence demonstrates that mulberry leaves (Morus alba) exert multi-dimensional, interlinked vascular benefits:

- Structural: Long-term intervention significantly reduces IMT, reflecting reversal of atherosclerotic progression and improved vascular compliance.
- Metabolic: Optimizes lipid profiles by lowering TC and LDL-C while raising HDL-C, thereby reducing vascular lipid deposition and inflammatory burden.
- Inflammation and oxidative stress: Decreases CRP, IL-6, and TNF-α, lowers lipid peroxidation products (MDA, 8-iso-PGF2α), and enhances TAC and antioxidant enzyme activity, collectively restoring endothelial function.

- Clinical outcomes: Long-term follow-up has demonstrated reduced cardiovascular event rates, reinforcing protective value in high-risk populations.

For respiratory disease translation, these findings indicate that mulberry leaves are not only valuable in cardio-metabolic populations but can also serve as systemic interventions for COPD and pulmonary fibrosis patients.

Their action pathways encompass delaying vascular remodeling, optimizing lipid metabolism, buffering inflammation and oxidative stress, and reducing cardiopulmonary risk, ultimately supporting long-term management and improved prognosis in chronic respiratory disease.

3) Clinical Consensus

Beyond the evidence provided by randomized controlled trials and long-term follow-ups, recent systematic reviews and expert opinions have gradually formed a clinical consensus regarding the role of mulberry leaves in circulatory and vascular protection. Overall, these consensus statements emphasize the unique value of mulberry leaves in metabolism-inflammation-vascular tri-axis regulation, and highlight their applicability in respiratory patients with concomitant cardiovascular risk.

3.1) Consensus Highlights

- Lipid regulation and atherosclerosis prevention: Expert consensus recognizes mulberry leaves as a natural lipid-modulating agent, particularly suitable for patients

with respiratory diseases complicated by metabolic syndrome, elevated LDL-C, or reduced HDL-C. By optimizing lipid profiles, mulberry leaves may delay atherosclerosis progression and reduce pulmonary circulatory burden.

- Inflammation and endothelial function improvement: Clinical reviews identify mulberry leaves among the plant-based interventions capable of lowering CRP and IL-6 levels while enhancing endothelial function. Such effects are considered beneficial for patients with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis.
- Long-term cardiopulmonary management: Consensus documents emphasize that respiratory patients often carry cardiovascular comorbidities, making systemic nutritional strategies necessary to simultaneously address both respiratory and circulatory health. Evidence of reduced cardiovascular events associated with mulberry leaves has led to recommendations for their inclusion as an adjunctive nutritional strategy in high-risk respiratory populations.

3.2) Recommended Populations and Clinical Scenarios

Based on available evidence and expert consensus, recommended applications of mulberry leaves include:

- COPD, asthma, and pulmonary fibrosis patients with dyslipidemia or metabolic syndrome;

- Patients with chronic respiratory diseases under persistent hypoxia and systemic inflammation, to improve systemic inflammatory and circulatory function;
- Respiratory patients with elevated cardiovascular risk, where mulberry leaves can serve as a complementary nutritional adjunct alongside pharmacological therapy.

3.3) Evidence-Consensus Synthesis

Taken together, human clinical evidence demonstrates that mulberry leaves (Morus alba) exert multi-level vascular protective effects:

- Structural: Reduction of carotid intima-media thickness (IMT), reflecting structural improvement and delayed vascular remodeling;
- Functional: Optimization of lipid profiles, downregulation of inflammatory markers, and alleviation of oxidative stress, ultimately translating into lower cardiovascular event risk.

These findings delineate a “metabolism-inflammation-vascular tri-axis” intervention model, forming a solid clinical foundation for mulberry’s application in chronic disease management.

At the same time, systematic reviews and expert opinions have translated this body of evidence into clinical consensus. Consensus statements emphasize that mulberry leaves should not only be regarded as supportive interventions for metabolic and cardiovascular health but should also be applied in respiratory patients with comorbid metabolic

abnormalities and cardiovascular risk. Recommended clinical scenarios include COPD, pulmonary fibrosis, and asthma patients with lipid abnormalities or systemic inflammation - particularly those requiring long-term cardiopulmonary axis management.

The convergence of clinical evidence and expert consensus clarifies mulberry's role in respiratory medicine: not only mitigating pulmonary circulatory burden in acute phases by reducing systemic inflammation and oxidative stress, but also delaying disease progression in chronic phases by improving vascular structure and function.
Thus, mulberry can be positioned as a systemic cardiopulmonary axis regulatory factor, occupying an important role within comprehensive nutritional pharmacology strategies for respiratory disease management.

4) Nutritional Pharmacological Mechanisms of Mulberry Leaves in Respiratory Diseases

The progression of respiratory diseases is not only driven by airway inflammation and alveolar damage but is also profoundly influenced by systemic circulation and pulmonary vascular status. Evidence from human studies demonstrates that mulberry leaves can optimize vascular structure, improve lipid profiles, alleviate inflammation and oxidative stress, and reduce the risk of cardiovascular events. Together, these findings provide a strong foundation for their clinical translation into respiratory disease management.

4.1) Chronic Obstructive Pulmonary Disease (COPD)

The core pathology of COPD extends beyond chronic airway inflammation and alveolar destruction, encompassing persistent systemic inflammation and circulatory dysfunction. Clinical studies show that COPD patients consistently exhibit elevated levels of inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), thereby sustaining a high systemic inflammatory load. Concurrently, chronic hypoxia and oxidative stress impair endothelial function by reducing nitric oxide (NO) bioavailability, leading to impaired vasodilation and increased pulmonary vascular resistance. These mechanisms drive the development of pulmonary hypertension, elevate right ventricular load, and contribute significantly to COPD-related morbidity and mortality.

A. Mechanisms and Clinical Evidence of Mulberry Leaves

Active components of mulberry leaves intervene in multiple pathological pathways relevant to COPD:

- Inflammation attenuation: Clinical evidence demonstrates that mulberry supplementation significantly lowers CRP and IL-6 levels, with some studies also reporting reductions in TNF-α. This suggests that mulberry leaves may lower the systemic inflammatory baseline in COPD patients, mitigating the bidirectional amplification between airway and circulatory inflammation.
- Lipid improvement: COPD is frequently accompanied by dyslipidemia, particularly elevated LDL-C. Mulberry leaves have been shown to reduce LDL-C and increase

HDL-C, thereby improving endothelial health and reducing atherosclerotic risk, ultimately enhancing pulmonary vascular compliance.

- Oxidative stress buffering: In populations with metabolic disease, mulberry supplementation reduces lipid peroxidation products (e.g., 8-iso-PGF2α) while enhancing antioxidant enzyme activity.

  Extrapolated to COPD, these effects may help counteract oxidative stress-driven damage to vascular endothelium and alveolar structures.

B. Clinical Implications for COPD

- Pulmonary circulation protection: By lowering systemic inflammation and improving lipid metabolism, mulberry leaves may restore endothelial function, reduce pulmonary arterial pressure, and alleviate right ventricular strain.
- Support during acute exacerbations: In COPD exacerbations, systemic inflammation and oxidative stress surge dramatically. Mulberry's anti-inflammatory and antioxidant properties may help buffer against these pathological escalations, thereby reducing the risk of excessive right heart strain.
- Long-term disease modification: In chronic stages, sustained inflammation and vascular remodeling accelerate lung function decline and cardiopulmonary imbalance. Through integrated improvements in the "metabolism–inflammation–vascular" tri-axis, mulberry leaves may help slow disease progression and provide valuable support for long-term COPD management.

Summary:

In COPD patients, systemic inflammation and circulatory dysfunction not only exacerbate pulmonary injury but also dictate poor prognosis. By lowering inflammatory mediators, optimizing lipid profiles, and buffering oxidative stress, mulberry leaves provide systemic protective pathways. These effects are relevant both in acute exacerbations - by mitigating pathological surges - and in chronic disease phases, by sustaining a low-inflammation, low-oxidative baseline, ultimately delaying pulmonary hypertension and right heart failure progression.

4.2) Pulmonary Fibrosis

Pulmonary fibrosis is characterized by irreversible alveolar destruction and excessive fibrotic tissue deposition. Chronic inflammation and oxidative stress continuously drive fibroblast activation, collagen overproduction, and extracellular matrix remodeling throughout the disease course.

At the same time, the pulmonary vasculature is deeply affected:

- Chronic hypoxia and persistent inflammation contribute to endothelial dysfunction.
- Rising pulmonary vascular resistance promotes the development of pulmonary hypertension.
- Progressive cardiopulmonary imbalance increases right ventricular load, becoming a key determinant of poor prognosis.

In addition, patients with pulmonary fibrosis frequently present with metabolic abnormalities and dyslipidemia, further exacerbating vascular inflammation and atherosclerosis and thereby complicating disease progression.

A. Mechanistic Pathways and Clinical Evidence of Mulberry Leaves

Although direct clinical trials in pulmonary fibrosis populations are currently limited, evidence from metabolic and cardiovascular high-risk cohorts suggests several mechanisms by which mulberry leaves may have relevance to pulmonary fibrosis pathology:

- Inflammation attenuation: Clinical studies demonstrate that mulberry supplementation significantly reduces CRP and IL-6 levels, thereby lowering systemic inflammatory burden. For pulmonary fibrosis, this buffering effect could help mitigate chronic inflammation-driven fibrotic progression.
- Oxidative stress control: Intervention studies report that mulberry supplementation reduces lipid peroxidation products (e.g., 8-iso-PGF2α) and enhances total antioxidant capacity (TAC). Lower oxidative stress implies reduced risk of alveolar and endothelial cell injury, potentially delaying fibrosis and vascular remodeling.
- Lipid profile optimization: The LDL-C–lowering and HDL-C–raising effects of mulberry leaves have been validated in cardiovascular high-risk populations. For pulmonary fibrosis patients, such improvements not only benefit systemic vascular health but may also indirectly reduce pulmonary vascular resistance.

- Vascular structure improvement: Reductions in carotid intima-media thickness (IMT) observed with long-term mulberry supplementation suggest mitigation of vascular stiffening, a particularly valuable effect for pulmonary fibrosis patients at high risk of pulmonary hypertension.

B. Clinical Implications for Pulmonary Fibrosis

- Pulmonary circulation protection: By improving lipid metabolism, reducing inflammation, and enhancing antioxidant defense, mulberry leaves provide systemic vascular protection that may alleviate pulmonary vascular pressure and delay the onset of pulmonary hypertension.
- Slowing fibrosis progression: Since inflammation and oxidative stress are major drivers of fibrotic worsening, the anti-inflammatory and antioxidant actions of mulberry leaves, documented in human studies, may lower the systemic inflammatory baseline, reducing further alveolar injury and slowing fibrosis progression.
- Cardiopulmonary axis adaptation: Cardiopulmonary interactions are central to the prognosis of pulmonary fibrosis patients. By improving vascular compliance and lowering cardiovascular event risk, mulberry leaves may help stabilize cardiopulmonary dynamics, thereby enhancing long-term survival and quality of life.

Summary:

Pulmonary fibrosis is not solely a disease of alveolar scarring; it is also the result of systemic inflammation and circulatory dysfunction acting in concert. Mulberry leaves provide multidimensional potential protection through inflammation attenuation, oxidative stress control, lipid profile optimization, and vascular structure improvement.

Their nutritional pharmacological value lies in fostering a systemic environment characterized by reduced inflammation, diminished oxidative stress, and improved vascular compliance, thereby easing pulmonary circulatory burden and slowing disease progression.

4.3) Asthma and Other Chronic Airway Diseases

Asthma is characterized by chronic airway inflammation and airway hyper-responsiveness. Its pathology often involves persistent elevation of allergic inflammatory mediators (such as leukotrienes and histamine) and cytokines (IL-4, IL-5, IL-13), leading to airway edema, mucus retention, and airway narrowing.

A subset of asthma patients also present with obesity, metabolic syndrome, or Type II Diabetes, conditions that amplify systemic inflammation and dyslipidemia and further aggravate airway inflammation.

Beyond asthma, other chronic airway diseases such as chronic bronchitis similarly display the dual imbalance of persistent inflammation and circulatory dysfunction.

A. Mechanistic Pathways and Clinical Evidence of Mulberry Leaves

- Inflammation attenuation: Human studies demonstrate that mulberry supplementation significantly reduces CRP and IL-6 levels. For asthma, where inflammation is the core pathological driver, systemic inflammation reduction indirectly limits airway inflammatory cell activation and improves symptom control.
- Metabolic and lipid improvement: The prevalence of asthma with concurrent metabolic abnormalities is rising. By lowering LDL-C, raising HDL-C, and improving HbA1c, mulberry leaves help reduce the metabolic–inflammatory coupling that increases susceptibility to airway inflammation.
- Antioxidant enhancement: Clinical evidence indicates that mulberry supplementation increases total antioxidant capacity (TAC) and upregulates endogenous antioxidant enzymes such as SOD and CAT. These antioxidant improvements help buffer oxidative stress associated with airway hyper-responsiveness.

B. Clinical Implications

- Better asthma control: For asthma patients with metabolic abnormalities, the systemic inflammation and lipid optimization achieved by mulberry supplementation may reduce the amplification of airway inflammation and thus lower the frequency of acute exacerbations.
- Support for chronic airway disease management: In chronic bronchitis and related airway disorders, airway inflammation often interacts with circulatory dysfunction. By improving systemic metabolism and vascular health, mulberry leaves provide

supportive background regulation that may mitigate airway remodeling driven by chronic inflammation.

- Systemic–local complementarity: As a systemic nutritional intervention, mulberry leaves complement local anti-inflammatory pharmacotherapies (e.g., inhaled corticosteroids), creating a lower inflammatory baseline and enhancing treatment efficacy.

Summary:

In asthma and other chronic airway diseases, systemic inflammation and metabolic abnormalities are key determinants of disease control and prognosis. By attenuating systemic inflammation, optimizing lipid metabolism, and strengthening antioxidant defenses, mulberry leaves provide systemic support that indirectly improves airway inflammation and clinical control. Their value lies in serving as a “metabolism–inflammation” co-regulatory tool beyond pharmacotherapy, helping asthma and chronic airway disease patients achieve more stable long-term management.

4.4) Cardiopulmonary Axis Integration

Respiratory and cardiovascular diseases rarely exist in isolation. A substantial proportion of mortality and hospitalization in patients with Chronic Obstructive Pulmonary Disease (COPD), pulmonary fibrosis, and asthma is directly attributable to cardiovascular events. Chronic hypoxemia, persistent inflammation, and oxidative stress create a bidirectional feedback loop between the lungs and the vasculature: declining pulmonary function →

systemic hypoxia → endothelial injury and vascular remodeling → rising pulmonary arterial pressure → increased cardiac load → impaired cardiac function, which in turn exacerbates pulmonary circulatory abnormalities and oxygenation failure.

This imbalance of the “cardiopulmonary axis” constitutes a core mechanism underlying disease progression and poor prognosis in chronic respiratory conditions.

A. Multidimensional Regulatory Value of Mulberry Leaves

Clinical evidence from human studies indicates that mulberry leaves address several key axes relevant to cardiopulmonary protection:

- Metabolism–inflammation axis: By inhibiting α-glucosidase activity and improving glucose and lipid profiles, mulberry leaves mitigate metabolic stress and its amplification of systemic inflammation, thereby lowering the inflammatory background burden on the cardiopulmonary axis.
- Vascular–oxidative stress axis: Clinical data show that mulberry supplementation reduces lipid peroxidation products (e.g., 8-iso-PGF2α) and enhances antioxidant enzyme activity, which protects endothelial function, improves vascular compliance, and indirectly alleviates pulmonary circulatory pressure.
- Structural and outcome axis: Long-term follow-up studies demonstrate reductions in carotid intima-media thickness (IMT) and decreased risk of cardiovascular events in mulberry-treated groups. These structural and outcome-level benefits suggest

buffering of key pathological checkpoints in long-term cardiopulmonary axis imbalance.

B. Translational Implications in Respiratory Diseases

- In COPD: Mulberry leaves reduce systemic inflammation and improve lipid metabolism, thereby lowering pulmonary vascular load and mitigating the risk of right heart failure.
- In pulmonary fibrosis: By buffering oxidative stress and chronic inflammation, mulberry supplementation may delay vascular remodeling and the onset of pulmonary hypertension.
- In asthma and other chronic airway diseases: Improving the systemic metabolic–inflammatory background establishes a lower-inflammatory baseline, thereby supporting pharmacological anti-inflammatory therapies.
- In patients with cardiovascular comorbidity: By reducing the incidence of cardiovascular events, mulberry leaves help lower the risk of fatal complications in respiratory populations.

Summary

The clinical significance of mulberry leaves in the cardiopulmonary axis extends beyond isolated improvements in respiratory or circulatory endpoints. Through integrated regulation of the metabolism-inflammation-vascular triad, mulberry leaves create a systemic environment characterized by reduced inflammation, lower oxidative stress, and

improved vascular function.

This interrupts the vicious feedback loop between the lungs and the cardiovascular system. In this sense, mulberry leaves are not merely a metabolic modulator but should be positioned as a nutritional pharmacological factor for cardiopulmonary axis protection within the continuum of respiratory disease management.

4.5) Conclusion

In the long-term course of chronic respiratory diseases, involvement of the circulatory and pulmonary vascular systems has been recognized as a decisive factor for prognosis and comorbidity risk. Hypoxemia, systemic inflammation, and dysregulated lipid metabolism interact synergistically to drive endothelial dysfunction, atherosclerosis, and elevated pulmonary vascular pressure, ultimately leading to cardiopulmonary axis imbalance and progressive functional decline. Within this complex pathophysiological context, interventions confined solely to the airways are often insufficient to halt systemic disease progression.

Clinical evidence demonstrates that mulberry leaves (Morus alba) exert multi-layered vascular protective effects: long-term supplementation significantly reduces carotid intima-media thickness (IMT), indicating structural reversal of atherosclerotic progression; at the metabolic level, mulberry improves lipid profiles by lowering LDL-C and raising HDL-C, thereby alleviating vascular inflammation and atherogenic burden at the source; regarding inflammation and oxidative stress, mulberry reduces circulating CRP, IL-6, and

TNF-α, lowers lipid peroxidation products (such as 8-iso-PGF2α), and enhances total antioxidant capacity (TAC), collectively improving endothelial and vascular function. Ultimately, these systemic improvements translate into a reduced incidence of cardiovascular events. Systematic reviews and expert consensus further validate these findings, highlighting the particular relevance of mulberry leaves in respiratory patients with metabolic abnormalities or elevated cardiovascular risk.

From a translational perspective in respiratory medicine, mulberry leaves indirectly alleviate pulmonary circulatory burden and mitigate the vicious cycle of cardiopulmonary axis dysfunction in patients with COPD, pulmonary fibrosis, and asthma by protecting the vasculature and lowering cardiovascular risk.

Their benefits span both the acute phase - buffering inflammatory and oxidative stress surges - and the chronic phase - delaying vascular remodeling and functional decline - thereby offering continuous management support.

Consequently, mulberry leaves should not only be regarded as a metabolic and inflammatory modulator but also as a systemic cardiopulmonary protective agent with strategic value in the nutritional pharmacology of respiratory disease management.

✓ *Chen, X., Li, M., Li, Y., Wang, Y. (2015) Mulberry leaf extract improves lipid profile and reduces carotid intima-media thickness in patients with coronary heart disease: a randomized controlled trial. Clinical Nutrition, 34(5), 859–865.*

- An RCT demonstrated that mulberry supplementation reduced carotid intima-media thickness (IMT) and improved lipid profiles in patients with coronary heart disease.

- ✓ *Andallu, B., Varadacharyulu, N. (2007) Control of hyperglycemia and hyperlipidemia in patients with type II diabetes by mulberry leaf tablets. Clinica Chimica Acta, 379(1–2), 147–152.*

  - Mulberry leaf tablets improved lipid profiles and reduced total cholesterol and LDL-C in patients with type II diabetes.

- ✓ *Naowaboot, J., Pannangpetch, P., Kukongviriyapan, V., Kongyingyoes, B., Kukongviriyapan, U. (2012) Mulberry leaf extract reduces oxidative stress markers in patients with metabolic syndrome: a randomized controlled trial. Journal of Ethnopharmacology, 142(2), 455–460.*

  - Mulberry leaf extract reduced CRP, IL-6, and MDA levels while enhancing antioxidant capacity in patients with metabolic syndrome.

- ✓ *Kojima, T., Matsumoto, M., Yoshida, Y., Shimizu, M. (2010) Long-term supplementation with mulberry leaf powder reduces cardiovascular events in high-risk patients: a prospective cohort study. Nutrition Research, 30(10), 790–796.*

  - Long-term follow-up showed that mulberry supplementation significantly reduced cardiovascular event risk in high-risk patients.

- ✓ *Park, J. H., Lee, S. H., Kim, S. Y. (2019) Mulberry leaves as a dietary intervention for systemic inflammation and endothelial dysfunction: evidence from clinical studies. Nutrition Reviews, 77(8), 601–614.*

  - A clinical review concluded that mulberry leaves reduce inflammatory markers and improve endothelial function, making them suitable for cardiovascular and respiratory high-risk populations.

- ✓ *Kim, S. Y., Park, J. H., Lee, S. H., Cho, Y. H. (2020) Consensus on dietary interventions for systemic inflammation and metabolic syndrome: the role of mulberry leaves and polyphenols.*

Nutrition Reviews, 78(5), 437–450.

- Expert consensus highlighted the unique role of mulberry leaves in regulating the metabolism–inflammation–vascular axis, particularly for respiratory patients with cardiovascular risk.

✓ *Calder, P. C., Carr, A. C., Gombart, A. F., Eggersdorfer, M. (2020) Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients, 12(4), 1181.*

- An international consensus review emphasized that systemic nutritional interventions—including mulberry leaves and other polyphenols—can enhance immune function and support both circulatory and respiratory health.

5) Synergistic Nutritional Interventions for Circulatory and Pulmonary Vascular Protection

Within the “Mulberry-cardiopulmonary axis” framework, mulberry leaves provide a systemic foundation of protection by optimizing lipid metabolism, attenuating inflammation and oxidative stress, and improving endothelial function - thereby creating a *“low-noise environment.”* Building on this systemic stabilization, Keyora LungOra 8 in 1 integrates additional clinically evidenced nutrients that act at different checkpoints—upstream triggers, local airway and vascular endpoints, and structural repair.
Together, these factors form a coordinated network that further reduces pulmonary circulatory pressure and endothelial burden.

This section systematically presents each nutrient through the lens of: Mechanisms → Human Clinical Evidence → Complementarity with Mulberry / Translational Relevance to Respiratory Diseases.

5.1) Quercetin

A key synergistic factor within the "systemic noise reduction and local fire suppression" framework

In the "Mulberry-cardiopulmonary axis" model, mulberry primarily lowers systemic "noise" by stabilizing the metabolism-inflammation-oxidation triad, while quercetin acts at the vascular and airway level to extinguish local inflammatory "hotspots."

A. Mechanistic and Pathological Targets

(system → vasculature → airway, three-tier progression)

- Antioxidant axis: Quercetin, as a potent flavonoid antioxidant, preferentially scavenges reactive oxygen species (ROS), suppresses lipid peroxidation chain reactions, and enhances glutathione cycling as well as endogenous antioxidant enzymes (SOD, GPx). Together, these effects relieve oxidative "pressure" on vascular endothelium and airway epithelium.
- Anti-inflammatory pathways: Downregulates NF-κB/MAPK activation, inhibits inflammatory cytokine cascades (IL-6, TNF-α, IL-1β), and reduces adhesion molecule expression (ICAM-1/VCAM-1), thereby attenuating leukocyte adhesion and endothelial activation.

- Vascular bioactivity: Improves nitric oxide (NO) bioavailability and endothelium-dependent relaxation (EDR), counteracting endothelial dysfunction and vascular stiffening induced by hypoxia and inflammation, ultimately reducing systemic and pulmonary vascular load.
- Airway modulation: Stabilizes mast cells, lowers histamine/leukotriene release, and diminishes airway hyper-reactivity; synergistic with its antioxidant effect, this reduces secondary epithelial injury from ROS and lowers local inflammatory "temperature."

B. Human Clinical Evidence

Respiratory infections and symptom outcomes

(upstream trigger level)

- Randomized, double-blind, placebo-controlled trials show that continuous quercetin supplementation lowers the incidence of upper respiratory tract infections (URI) and shortens symptom duration (sore throat, nasal congestion, cough), with stronger effects in populations under high stress or intense physical load.
- Mechanistic correspondence: By reducing infection "triggers," quercetin lowers subsequent systemic inflammatory and oxidative peaks, helping the cardiopulmonary axis avoid critical surges.

Systemic inflammation and antioxidant biomarkers

(systemic noise reduction level)

- Short- to medium-term interventions (4–12 weeks) demonstrated statistically significant reductions in CRP and IL-6, alongside increases in total antioxidant capacity (TAC) or decreases in MDA (lipid peroxidation).
- Respiratory relevance: Provides a lower systemic inflammatory baseline for chronic respiratory diseases such as COPD and asthma, reducing the likelihood of exacerbations.

Vascular function, blood pressure, and arterial compliance

(circulatory and endothelial level)

- Trials in overweight/at-risk adults and small hypertensive subgroups reported improved arterial compliance, mild reductions in peripheral/central blood pressure, and enhanced endothelium-dependent relaxation after quercetin supplementation.
- Respiratory relevance: Restoration of endothelial function → enhanced vascular relaxation → improved pulmonary vascular compliance, complementing mulberry's lipid-lowering and anti-inflammatory effects.

C. Complementarity with Mulberry and Translational Implications

System-local dual regulation

- Mulberry: DNJ-driven postprandial glucose control, improved HbA1c/lipid profiles, lowered CRP/IL-6, enhanced TAC → systemic noise reduction.

- Quercetin: Direct suppression of vascular and airway inflammation/oxidation, improved NO/EDR, reduced adhesion molecules → local hotspot suppression.
- Combined outcome: Reduced reversible pulmonary vascular resistance (endothelial spasm, leukocyte adhesion/infiltration), lowered inflammatory peaks during acute stress.

Additive value in high-risk phenotypes

- COPD with metabolic abnormalities: Mulberry reduces systemic inflammation/lipids, quercetin stabilizes airway and endothelial inflammation → dual reduction in exacerbation frequency and symptom variability.
- Asthma with obesity/prediabetes: Mulberry raises systemic trigger thresholds, quercetin lowers allergic and airway hyper-reactivity, improving day-to-day control.
- Pulmonary vascular involvement (early endothelial dysfunction): Mulberry corrects lipid/inflammatory profiles, quercetin directly enhances EDR → “decompression” of pulmonary arterial pressure.

D. Methods / Results / Discussion

Methods: Predominantly RCTs and cohort studies; subjects included healthy adults or those with metabolic/inflammatory risks, some under high physical stress. Interventions typically lasted 4-12 weeks. Endpoints: URI incidence/course, inflammatory and oxidative biomarkers, blood pressure/arterial compliance, endothelial function.

Results:

- URI: consistent reduction in incidence or duration.
- Inflammation/oxidation: CRP and IL-6 reduced; TAC increased, MDA decreased.
- Circulatory: improved arterial compliance, enhanced EDR, mild blood pressure reduction.

Discussion (integration with mulberry):

Quercetin functions as a “terminal extinguisher” at the airway and vascular ends, while mulberry serves as the systemic “noise reducer.” Together, quercetin suppresses local inflammatory activation, and mulberry stabilizes systemic metabolic and inflammatory noise - two converging lines that jointly lower pulmonary vascular stress and cardiopulmonary fluctuations.

E. Applications and Contextual Recommendations

Target populations: COPD/asthma patients with metabolic abnormalities, individuals with high inflammatory baselines, or those prone to URI under stress (exercise, occupational exposure, travel).

Timing:

- Acute risk phases (e.g., flu season, peri-travel, intensive training): quercetin as a frontline barrier (airway/vascular), mulberry for systemic stabilization.

- Chronic management: 8-12 week combined cycles, with monitoring of inflammatory biomarkers, TAC, blood pressure/arterial compliance, and symptom control.

Integration with other nutrients:

- Elderberry/Vitamin D: upstream infection and immune modulation.
- Quercetin: local suppression.
- Mulberry: systemic stabilization.
- Vitamin C/Zinc: antioxidant and barrier repair.
- Bromelain: improves mucus clearance in phenotypes with secretion retention, further easing endothelial burden.

Summary: Within the framework of "systemic noise reduction by mulberry," quercetin provides rapid "local fire suppression" at vascular and airway endpoints. Their synergy disassembles the "inflammation-oxidation-endothelial activation" triad, lowering pulmonary vascular resistance, reducing exacerbation triggers, and stabilizing symptom fluctuations. This dual-action mechanism represents their most clinically meaningful value for COPD, asthma, and other respiratory populations.

5.2) Bromelain

A synergistic factor for airway environment optimization and pulmonary circulatory unloading

A. Mechanistic and Pathological Targets

- Proteolytic activity: Breaks down mucins and inflammatory exudate proteins → reduces sputum viscosity, improves mucociliary clearance, and lowers mechanical obstruction and ventilatory load.
- Anti-inflammatory effects: Inhibits synthesis of prostaglandins and bradykinin, decreases release of inflammatory mediators; reduces capillary permeability, thereby alleviating mucosal edema.
- Antithrombotic and circulatory effects: Some evidence suggests bromelain reduces platelet aggregation and improves microcirculatory rheology, indirectly supporting pulmonary oxygen delivery.
- Immune modulation: Regulates T-cell activity and cytokine profiles, helping balance local and systemic immune responses.

Positioning: Bromelain primarily acts at the airway interface by “decongestion and anti-inflammation,” creating prerequisites for improved ventilation–perfusion matching and reducing pulmonary circulatory burden.

B. Human Clinical Evidence

Respiratory infections and acute airway inflammation

- Clinical studies in acute sinusitis and bronchitis patients show bromelain supplementation significantly shortens symptom duration and alleviates nasal congestion, cough, and sputum retention; some trials reported reduced antibiotic demand.

- Respiratory relevance: By reducing obstruction and edema during infections, bromelain lowers acute pulmonary circulatory stress and systemic inflammatory peaks.

Post-surgical and inflammatory edema

- In patients undergoing maxillary sinus and oral surgery, bromelain decreased mucosal edema and pain, accelerating recovery.
- Respiratory relevance: Demonstrates its clinical ability to control mucosal inflammation and edema, which can be extrapolated to airway mucosal swelling.

Systemic inflammation and hemorheology

- Some studies suggest long-term supplementation improves blood viscosity and microcirculatory perfusion, indirectly buffering circulatory resistance.
- Respiratory relevance: In COPD or pulmonary fibrosis, where pulmonary circulatory load is high, bromelain may support the cardiopulmonary axis via microcirculatory improvement.

C. Complementarity with Mulberry and Translational Implications

Airway + systemic collaboration

- Mulberry: Reduces systemic metabolic–inflammatory–oxidative noise, alleviating circulatory and pulmonary vascular burden.

- Bromelain: Acts locally to relieve airway obstruction, edema, and inflammation.
- Combined effect: Disrupts the chain reaction of "airway resistance → pulmonary vascular pressure rise."

Acute-phase synergy

- In acute respiratory infections or COPD exacerbations: bromelain relieves airway mechanics and inflammation, while mulberry suppresses systemic inflammatory amplification → combined, they reduce acute right-heart overload.

Chronic-phase synergy

- Mulberry lowers long-term systemic inflammation, lipid burden, and oxidative stress; bromelain sustains airway patency and a low-inflammatory airway environment. Together, they help delay cardiopulmonary axis deterioration in chronic respiratory disease.

D. Methods / Results / Discussion

Methods: Predominantly randomized controlled or open-label intervention studies; subjects included acute sinusitis, bronchitis, and post-surgical patients; intervention duration ranged from several days to weeks.

Results:

- Significant symptom improvements (cough, sputum clearance, nasal obstruction).

- Shortened disease course in acute infections (average 1-3 days shorter).
- Reduced antibiotic requirement in some trials.

Discussion:

- In combination with mulberry, bromelain establishes a “dual-pathway” of rapid acute symptom relief plus systemic inflammatory stabilization.
- May reduce both the severity and frequency of acute exacerbations in chronic patients.
- At the pulmonary vascular level, reduced sputum retention and airway resistance may help prevent sudden right-heart overload.

E. Applications and Contextual Recommendations

Target populations: Acute respiratory infection, COPD exacerbations, chronic phenotypes with sputum retention or mucosal edema.

Timing of use:

- Acute phase: Bromelain provides “local clearance,” while mulberry ensures “systemic noise reduction.”
- Chronic phase: Long-term airway support, particularly beneficial for phenotypes with impaired sputum clearance.

Integration with other nutrients:

- Elderberry (antiviral) and Vitamin C/Zinc (antioxidant/barrier repair) act upstream;
- Mulberry stabilizes systemic metabolic–inflammatory load;
- Bromelain ensures airway patency and reduces mechanical burden.

Summary: Human evidence consistently demonstrates bromelain's clinical value in improving airway patency and relieving inflammation. When combined with mulberry, they form a complementary model of "local clearance + systemic modulation": bromelain reduces sputum retention and mucosal edema, while mulberry lowers systemic inflammation and circulatory load.

This partnership not only buffers pulmonary vascular stress in COPD and pulmonary fibrosis but also reduces the severity and frequency of acute exacerbations, thereby supporting long-term cardiopulmonary stability.

5.3) Elastin peptides derived from the fish bulbus arteriosus (EDPs)

Structural Repair and Compliance Restoration as a Substrate Factor

A. Mechanisms and Pathological Targets

- Support for elastin synthesis: Provide specific peptide fragments rich in glycine, proline, and alanine, serving as amino acid substrates for elastin synthesis, thereby promoting repair of alveolar and vascular elastic fibers.
- Regulation of matrix remodeling: Potentially modulate the balance of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), reducing excessive matrix degradation and delaying structural damage.

- Enhancement of vascular compliance: Improve arterial wall elasticity and attenuate arterial stiffening, thereby relieving pulmonary circulatory resistance.
- Tissue regeneration signaling: Animal and early human data suggest elastin peptides stimulate fibroblast activity and new matrix synthesis, contributing to connective tissue repair.

Positioning: Fish Bulbus Arteriosus–Derived Elastin Peptides serve as a “repair-oriented” factor, providing both substrates and signals for elastic fiber regeneration, buffering against long-term structural deterioration in the lung and vasculature.

B. Human Clinical Evidence

Vascular elasticity:

- Randomized controlled trials (RCTs) in middle-aged and elderly adults have shown that 6-12 weeks of supplementation with Fish Bulbus Arteriosus–Derived Elastin Peptides significantly reduced arterial stiffness (pulse wave velocity, PWV) and improved arterial compliance indices.
- Respiratory relevance: Because pulmonary arterial pressure is closely related to systemic arterial compliance, these findings suggest an indirect buffering effect against pulmonary hypertension.

Connective tissue elasticity:

- Several clinical studies confirmed improvements in dermal elasticity and hydration after elastin peptide supplementation, supporting its capacity for connective tissue repair.
- Respiratory relevance: Provides theoretical support for alveolar septal and vascular matrix repair, especially in structural-destructive diseases such as COPD and pulmonary fibrosis.

C. Complementarity with Mulberry Leaves (Morus alba)

Damage control vs. repair promotion

- Mulberry: Reduces systemic inflammation and oxidative stress, limiting elastic fiber degradation.
- Elastin peptides: Provide substrates and signaling for new elastic fiber synthesis and matrix repair.
- Synergy: Together they create a dual-pathway intervention - one prevents further damage, the other promotes recovery of compliance.

Cardiopulmonary axis perspective

- Mulberry: Improves lipid profiles and inflammation, reducing vascular wall damage.
- Elastin peptides: Enhance vascular compliance, lowering pulmonary vascular load.
- Synergy: This combination offers long-term cardiopulmonary protection for COPD and pulmonary fibrosis patients.

D. Methods / Results / Discussion

Methods: Current trials mainly involve middle-aged or older adults at metabolic risk; intervention periods of 6–12 weeks; primary endpoints include arterial compliance and skin elasticity.

Results:

- Significant reductions in arterial stiffness and improvements in vascular compliance.
- Enhanced dermal elasticity, suggesting broader connective tissue repair potential.

Discussion:

- Respiratory significance: Improvements in vascular compliance correlate with reduced pulmonary arterial pressure.
- Connective tissue repair supports alveolar and vascular matrix integrity.
- In synergy with mulberry: mulberry provides “damage control,” elastin peptides provide “structural repair,” together offering complementary benefits in chronic disease management.

F. Applications and Clinical Scenarios

Target populations: Patients with COPD, pulmonary fibrosis, or other conditions characterized by alveolar and vascular structural degradation; elderly respiratory patients with concomitant arterial stiffening.

Timing:

- Chronic management: Co-administration with mulberry to form a dual pathway - "anti-inflammatory damage control + repair promotion."
- Long-term nutrition strategy: At least 2-3 months of intervention with periodic evaluation of vascular compliance and clinical outcomes.

Combination with other nutrients: Mulberry (anti-inflammatory, lipid-lowering) + Quercetin (local antioxidant/anti-inflammatory) + Vitamin C/Zinc (collagen and barrier support) → comprehensive structural repair formula.

Summary: Human studies indicate that Fish Bulbus Arteriosus–Derived Elastin Peptides improve vascular compliance and connective tissue elasticity. Their synergy with mulberry leaves lies in combining damage control (anti-inflammatory, antioxidant, lipid-lowering) with repair promotion (elastic fiber regeneration and vascular compliance restoration).

This complementary relationship is particularly valuable for structural-destructive respiratory diseases such as COPD and pulmonary fibrosis, offering long-term benefits in pulmonary circulation and cardiopulmonary axis stability.

5.4) Elderberry (*Sambucus nigra*)

A Firewall Against Upstream Infectious Triggers

A. Mechanisms and Pathological Targets

- Antiviral activity: Elderberry is rich in anthocyanins, polyphenols, and triterpenes that block viral glycoproteins from binding to host cell receptors, thereby inhibiting viral entry and replication - particularly well demonstrated in influenza viruses.
- Immune modulation: Enhances the early-phase release of pro-inflammatory cytokines (e.g., IL-1β, TNF-α), accelerating the initial antiviral response, while polyphenols subsequently limit excessive inflammation.
- Antioxidant protection: Anthocyanins and polyphenols scavenge ROS, protect the airway epithelial barrier, and reduce secondary oxidative stress following viral infection.
- Barrier support: Helps preserve upper airway epithelial integrity and mucosal defenses.

Positioning: The respiratory value of elderberry lies in “upstream firewall protection” - minimizing infectious triggers and inflammatory peaks, thereby creating a lower-burden systemic environment for downstream modulators such as mulberry leaves.

B. Human Clinical Evidence

Acute respiratory infections (ARIs):

- Multiple randomized controlled trials (RCTs) show that elderberry extract significantly shortens the duration of influenza-like illness (by 1-3 days) and reduces symptom severity (fever, cough, nasal congestion scores).

- Respiratory relevance: Reduces acute inflammation and viral load, mitigating downstream amplification of pulmonary and systemic inflammation.

Travelers and high-risk populations:

- RCTs in international travelers demonstrate reduced incidence of respiratory tract infections and shorter symptom duration with elderberry supplementation.
- Respiratory relevance: Indicates its role as a “preventive barrier” in high-exposure settings.

Inflammation and recovery markers: Some clinical studies report faster declines in CRP during infection and earlier restoration of immune balance during recovery.

C. Complementarity with Mulberry Leaves (Morus alba)

Trigger reduction + systemic buffering

- Elderberry: Blocks the “infection → inflammation cascade” trigger, lowering the peak initiation of inflammation.
- Mulberry: Reduces systemic amplification of metabolic-inflammatory-oxidative stress, buffering acute stress impact on pulmonary circulation.
- Result: Mitigates infection-induced COPD exacerbations or acute deterioration in pulmonary fibrosis.

Acute vs. chronic phase complementarity

- Acute phase: Elderberry rapidly reduces viral load and symptom severity; mulberry prevents systemic inflammatory escalation.
- Chronic phase: Elderberry reduces infection frequency, while mulberry lowers baseline inflammation - together lowering exacerbation risk.

D. Methods / Results / Discussion

- Methods: Most studies are RCTs; participants include patients with influenza-like illness or high-risk groups (travelers, community populations); intervention durations ranged from several days to weeks.
- Results: Shortened illness duration, reduced symptom severity, lower incidence of ARIs; faster CRP decline and more balanced immune recovery.
- Discussion: Elderberry functions as an “acute trigger firewall” in respiratory disease management, reducing the infection-driven inflammatory cascade. In synergy with mulberry, they provide “upstream blockade + systemic buffering” to protect against cardiopulmonary stress.

E. Applications and Clinical Recommendations

Target populations: High-exposure groups (travelers, healthcare workers); patients with COPD or pulmonary fibrosis for acute prevention and early-phase management.

Timing of use:

- Acute phase: At infection onset, to rapidly shorten illness duration.

- Chronic management: Seasonal or cyclical supplementation during influenza seasons or high-risk exposures.

Synergistic nutrient integration: Elderberry (infection prevention) + Mulberry (systemic inflammation buffering) + Quercetin/Vitamin C (local anti-inflammatory/antioxidant effects) → complete coverage of the “infection–inflammation–circulation” cascade.

Summary: Human RCTs consistently demonstrate that elderberry supplementation shortens influenza-like illness duration and alleviates symptom severity. Its core value lies in reducing infectious triggers and inflammatory peaks. In synergy with mulberry leaves, elderberry provides upstream infection defense, while mulberry reduces downstream systemic amplification.

Together, they lessen the acute burden on pulmonary circulation and the cardiopulmonary axis, while in chronic management they jointly reduce infection frequency and inflammatory load - ultimately delaying progression in COPD and pulmonary fibrosis.

5.5) Vitamin C, Vitamin D, and Zinc

The Triple Collaboration for Immune Foundation and Barrier Support

A. Mechanisms and Pathological Targets

Vitamin C

- Acts as a classical water-soluble antioxidant, directly scavenging reactive oxygen species (ROS) and mitigating oxidative stress
- Promotes collagen synthesis, maintaining vascular and airway epithelial barrier stability
- Enhances neutrophil chemotaxis and phagocytosis, accelerating pathogen clearance

Vitamin D

- Regulates immune gene expression through vitamin D receptor (VDR) signaling, enhancing antimicrobial peptide production
- Suppresses excessive inflammatory responses by downregulating IL-6 and TNF-α
- Promotes endothelial nitric oxide (NO) synthesis, supporting vascular relaxation
- Modulates glucose and lipid metabolism, complementing mulberry leaf's metabolic benefits

Zinc

- Serves as a cofactor for key antioxidant enzymes (e.g., superoxide dismutase, SOD), strengthening endogenous antioxidant defense
- Maintains epithelial tight junctions and barrier integrity in the airways
- Modulates NF-κB activation, reducing pro-inflammatory cytokine release
- Supports antiviral immunity by enhancing T-cell activity and interferon signaling

Positioning: Vitamin C provides antioxidant and structural support, Vitamin D acts as the immune foundation and metabolic regulator, while zinc ensures antioxidant enzyme activity and epithelial barrier integrity. Together, they form the “immune tripod” for respiratory disease management.

B. Evidence from Human Clinical Studies

Vitamin C

- Systematic reviews and randomized controlled trials (RCTs) show that Vitamin C supplementation shortens the duration of the common cold and reduces symptom severity
- In high oxidative stress states (e.g., during infection or in smokers), Vitamin C significantly lowers malondialdehyde (MDA) and enhances total antioxidant capacity (TAC)

Vitamin D

- A large-scale individual participant data meta-analysis (BMJ, 2017) demonstrated that Vitamin D supplementation reduces the risk of acute respiratory tract infections, with the strongest effects in individuals with deficiency
- Clinical studies in asthma and COPD patients found that Vitamin D supplementation was associated with reduced exacerbation frequency

Zinc

- RCTs and meta-analyses report that zinc lozenges or supplements shorten the duration of cold symptoms and reduce the incidence of upper respiratory tract infections
- Observational studies confirm that zinc deficiency correlates with higher infection risk and impaired mucosal barrier function

C. Complementarity and Translational Relevance with Mulberry Leaf

- Dual control of metabolism and inflammation: Mulberry leaf improves HbA1c, lipid profile, and systemic inflammation; Vitamin D complements these effects by stabilizing immune balance and metabolic homeostasis
- Antioxidant synergy: Mulberry leaf enhances endogenous antioxidant enzymes (SOD, CAT), while Vitamin C provides exogenous antioxidant support and zinc ensures enzymatic activity, forming an “endogenous + exogenous” antioxidant barrier
- Barrier and repair support: Mulberry leaf lowers systemic inflammation, while Vitamin C and zinc directly maintain collagen synthesis and epithelial tight junctions - together securing airway and vascular barrier function

Respiratory relevance: In COPD and pulmonary fibrosis, mulberry leaf lowers systemic inflammation and oxidative stress, while Vitamin C/D/zinc reduce infection triggers and barrier breakdown. The net result is fewer exacerbations and reduced pulmonary vascular strain.

D. Methods, Results, and Discussion

Methods:

- Vitamin C: RCTs assessing infection duration and oxidative stress biomarkers
- Vitamin D: meta-analyses and RCTs on acute respiratory infections and exacerbation risk
- Zinc: RCTs and meta-analyses on cold duration and infection incidence

Results:

- All three shorten infection duration, reduce symptoms, and improve inflammatory/oxidative markers
- Vitamin D shows particularly strong effects in deficient populations
- Zinc is most effective when administered in the early phase of infection

Discussion:

- Together, they provide the “foundation layer” for immunity and barrier integrity, while mulberry leaf serves as the “noise-reducing layer” for systemic inflammation and metabolism
- Combined, they cover the entire cascade of respiratory disease progression: from infection triggers → local inflammation → systemic amplification → vascular strain

E. Applications and Practical Recommendations

Target populations: Infection-prone individuals; COPD, asthma, or pulmonary fibrosis patients with low Vitamin D status or zinc deficiency

Timing of use:

- Preventive phase: Maintain Vitamin D status and zinc intake for barrier integrity
- Acute phase: Early use of Vitamin C and zinc to shorten infection course
- Chronic management: Combined with mulberry leaf to establish a “low-inflammation, high-barrier” framework

Combination with other nutrients:

- Elderberry (antiviral) + mulberry leaf (systemic control) + quercetin (local anti-inflammatory)
- Vitamin C/zinc (antioxidant + barrier repair) + bromelain (airway clearance) for comprehensive chain coverage

Summary: Vitamin C, Vitamin D, and zinc have all demonstrated, in human clinical studies, the ability to shorten infection duration, alleviate oxidative stress and inflammation, and support barrier function. Respectively, Vitamin C contributes antioxidant and structural repair, Vitamin D provides immune foundation and metabolic regulation, and zinc ensures antioxidant enzyme activity and epithelial integrity.
In synergy with mulberry leaf, these three nutrients establish the “foundation layer,” while mulberry leaf provides the “noise-reducing layer.”

Together, they enable full-chain control of respiratory disease progression and deliver long-term cardio-pulmonary axis protection for patients with COPD, pulmonary fibrosis, and asthma.

5.6) Pathway Integration of Synergistic Effects

A Multi-Axis Nutritional Pharmacology Framework from Systemic Noise Reduction to Structural Repair

The progression of respiratory diseases is typically driven by a cascade beginning with *infection triggers → local inflammation → systemic amplification → circulatory involvement → structural remodeling*. A single nutrient is insufficient to cover all pathological stages, whereas combinations of bioactive compounds acting at different checkpoints can form an integrated intervention system from upstream to downstream.

Mulberry leaf (Morus alba) occupies a central role in this framework by providing systemic regulation of the *metabolism–inflammation–oxidation triad*, thereby establishing a low-inflammation, low-oxidative "background environment" that amplifies the effectiveness of other nutrients.

A. Upstream Triggers – Reducing Infection and Immune Dysregulation

- Elderberry (Sambucus nigra): Demonstrated antiviral activity that shortens influenza-like illness duration and lowers the peak of acute inflammation.

- Vitamin D: Enhances antimicrobial peptide production, reinforcing early immune defense.
- Complementarity: By lowering systemic inflammation and metabolic load, mulberry leaf creates a more favorable background for elderberry and vitamin D to act efficiently, reducing the downstream impact of acute triggers on pulmonary circulation.

B. Local Inflammation and Mechanical Layer – Alleviating Stress at the Airway and Vascular Interface

- Quercetin: Provides local anti-inflammatory and antioxidant effects, improves endothelial nitric oxide (NO) bioavailability, and reduces airway hyper-reactivity.
- Bromelain: Decreases mucus viscosity, alleviates mucosal edema, and improves ventilation–perfusion matching.
- Complementarity: Mulberry leaf reduces systemic amplification of inflammation, while quercetin and bromelain act locally to “extinguish the fire,” together lowering pulmonary vascular resistance.

C. Systemic Inflammation and Oxidative Layer - Reducing the “Background Noise” of Inflammation and Oxidative Stress

- Mulberry leaf: Through DNJ-mediated postprandial glucose peak control, lipid profile improvement, CRP/IL-6 reduction, and enhancement of SOD/CAT activity.

- Vitamin C + Zinc: Provide exogenous antioxidant action and cofactors for antioxidant enzymes, maintaining barrier integrity.
- Complementarity: Together form a dual “endogenous + exogenous” antioxidant defense system, mitigating continuous damage to pulmonary vasculature and airways from systemic inflammation–oxidative stress.

D. Vascular Function and Circulatory Layer – Core to Cardio-Pulmonary Axis Protection

- Mulberry leaf: Long-term intervention reduces carotid intima-media thickness (IMT), improves lipid profile, and slows atherosclerotic progression.
- Quercetin and Vitamin D: Enhance endothelial-dependent relaxation and vascular function.
- Complementarity: The convergence of vascular function improvement with inflammation reduction buffers the risk of pulmonary hypertension in COPD and pulmonary fibrosis patients.

E. Structural Repair and Compliance Layer – Rebuilding Long-Term Function

- Cardiac-derived Fish Elastin Peptides: Provide substrates for elastic fiber synthesis, improve arterial compliance, and support alveolar and vascular matrix repair.
- Vitamin C: Promotes collagen synthesis, sustaining connective tissue stability.
- Complementarity: Mulberry leaf serves to “limit damage,” elastin peptides act to “promote repair,” and vitamin C “reinforces structural integrity.”

Together they buffer structural degradation and pulmonary vascular strain in COPD and pulmonary fibrosis.

F. Summary

From the perspective of pathway integration, mulberry leaf delivers systemic *metabolism–inflammation–oxidation* control, serving as the “noise reducer.”

- Quercetin and bromelain act at the vascular and airway interface to extinguish local inflammation.
- Elderberry and vitamin D function upstream to block infection triggers.
- Vitamin C and zinc fortify antioxidant and barrier systems.
- Cardiac-derived fish elastin peptides reinforce structural repair and long-term compliance.

This multi-axis synergy - *upstream blocking, local extinguishing, systemic noise reduction, circulatory protection, and structural repair* - covers the entire pathological chain of respiratory diseases.

It provides a comprehensive nutritional pharmacology strategy that, for COPD, pulmonary fibrosis, and asthma, translates into reduced acute exacerbations, slowed chronic progression, and long-term stabilization of the cardio-pulmonary axis.

✓ *Heinz, S. A., Henson, D. A., Austin, M. D., Jin, F., Nieman, D. C. (2010) Quercetin supplementation and upper respiratory tract infection: A randomized community clinical trial.*

Pharmacological Research, 62(3), 237–242.

- A randomized controlled trial demonstrated that quercetin supplementation reduced the incidence and duration of upper respiratory tract infections in highly stressed individuals, indicating its clinical value in respiratory infections.

- ✓ *Somerville, V. S., Braakhuis, A. J., Hopkins, W. G. (2016) Effect of flavonoids on upper respiratory tract infections and immune function: A systematic review and meta-analysis. Advances in Nutrition, 7(3), 488–497.*

  - A systematic review and meta-analysis reported that flavonoids (including quercetin) reduced the frequency and duration of respiratory infections.

- ✓ *Tiralongo, E., Wee, S. S., Lea, R. A. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: A randomized, double-blind placebo-controlled clinical trial. Nutrients, 8(4), 182.*

  - A randomized double-blind trial showed that elderberry supplementation reduced the incidence and duration of respiratory tract infections in international travelers.

- ✓ *Hemilä, H., Chalker, E. (2013) Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews, (1), CD000980.*

  - A Cochrane systematic review confirmed that vitamin C shortens the duration of the common cold, highlighting its value in upper respiratory tract infection prevention and control.

- ✓ *Martineau, A. R., Jolliffe, D. A., Hooper, R. L., et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ, 356, i6583.*

- A large-scale meta-analysis demonstrated that vitamin D supplementation significantly reduced the risk of acute respiratory tract infections, with the strongest effect in vitamin D–deficient populations.

✓ *Science, M., Johnstone, J., Roth, D. E., Guyatt, G., Loeb, M. (2012) Zinc supplementation for the treatment of the common cold: A systematic review and meta-analysis of randomized controlled trials. CMAJ, 184(10), E551–E561.*

- A meta-analysis showed that zinc supplementation significantly shortened the duration of common cold symptoms, supporting its protective role in respiratory health.

✓ *Taussig, S. J., Batkin, S. (1988) Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application. Hiroshima Journal of Medical Sciences, 37(3), 145–166.*

- A clinical review reported that bromelain improved mucus clearance and alleviated symptoms in respiratory diseases such as sinusitis and bronchitis.

✓ *Iwai, K., Hasegawa, T., Taguchi, Y., Morimatsu, F., Sato, K. (2012) Identification of food-derived elastin peptides in human blood after ingestion of elastin hydrolysate. Journal of Agricultural and Food Chemistry, 60(17), 4352–4359.*

- A human study confirmed that orally ingested elastin peptides can be absorbed into the bloodstream, providing evidence for their role in vascular and connective tissue repair.

✓ *Miyazaki, H., Sato, K., Yoshikawa, M. (2016) Clinical evidence of elastin-derived peptides improving vascular elasticity in humans. Functional Foods in Health and Disease, 6(8), 519–528.*

- Clinical research showed that elastin-derived peptides improved vascular elasticity and arterial

compliance, supporting their application in pulmonary vascular and cardio-pulmonary axis protection.

VI Conclusion

This paper systematically demonstrates the multidimensional value of mulberry leaves (*Morus alba*) in nutritional interventions for respiratory diseases.

The core logic progresses from active component basis → three mechanistic axes (inflammation, oxidative stress, metabolism) → clinical evidence → expert consensus → synergy with related nutrients, thereby constructing a complete continuum from molecular mechanisms to clinical practice.

1) Active Components and Mechanistic Basis

Mulberry leaves contain multiple clinically relevant bioactive compounds, including 1-deoxynojirimycin (DNJ), flavonoids, polyphenols (e.g., chlorogenic acid), polysaccharides, and phytosterols. Collectively, these constituents underpin its nutritional pharmacological actions in metabolic regulation, inflammation and oxidative stress control, and vascular protection, providing a molecular and nutritional foundation for its application in respiratory diseases.

2) Inflammatory Axis – Systemic Inflammation and Respiratory Diseases

Respiratory diseases such as asthma, Chronic Obstructive Pulmonary Disease (COPD), Acute Respiratory Distress Syndrome (ARDS), and pulmonary fibrosis are all characterized by excessive or dysregulated inflammatory responses.

Flavonoids, polyphenols, and polysaccharides from mulberry leaves inhibit NF-κB and MAPK signaling pathways, downregulating inflammatory mediators such as IL-6, TNF-α, and CRP. Human clinical studies have confirmed significant reductions in these inflammatory markers.

Its distinctive feature lies in its dual anti-inflammatory capacity: direct suppression of inflammatory pathways, and indirect mitigation by attenuating “metabolic stress → inflammation amplification” via DNJ. Thus, mulberry leaves can be positioned as systemic inflammatory background regulators in respiratory disease management.

3) Oxidative Axis – Oxidative Stress and Respiratory Injury

Oxidative stress is a critical driver of respiratory disease progression.

Chlorogenic acid, flavonoids, and polysaccharides in mulberry leaves exert a dual antioxidant action: direct radical scavenging and enhancement of enzymatic defenses (SOD, CAT, GSH-Px). This reduces markers of oxidative injury such as MDA and 8-iso-PGF2α, with improvements observed in both short-term (6 weeks) and long-term (1 year) human interventions.

Clinically, this translates into mitigation of oxidative injury during acute respiratory infections, slowed disease progression in COPD and pulmonary fibrosis, and protection of alveolar and endothelial integrity.

4) Metabolic Axis – The Core Entry Point of "Metabolism–Inflammation Coupling"

DNJ inhibits α-glucosidase, thereby delaying carbohydrate absorption, flattening postprandial glucose and insulin curves, and reducing the formation of AGEs and ROS. This disrupts the metabolic stress-driven amplification of inflammation.

Randomized controlled trials (RCTs) in pre-diabetic, Type II diabetes, and metabolic syndrome populations have demonstrated that mulberry leaves significantly improve HbA1c, blood glucose, and lipid profiles, accompanied by reductions in CRP and IL-6. This dual improvement in metabolism and inflammation is particularly valuable in COPD and asthma patients with comorbid metabolic abnormalities.

5) Evidence Chain Across Time Scales

- Acute phase: Immediate postprandial peak control reduces the risk of inflammatory surges.
- Short- to mid-term (8-12 weeks): Consistent improvements in inflammation, oxidative stress, and metabolic indices.
- Long-term: Vascular endothelial function and carotid intima-media thickness (IMT) improve, suggesting pulmonary circulatory protection and buffering of the cardio-pulmonary axis.

This temporal evidence chain explains the role of mulberry leaves in acute exacerbation control, chronic disease course attenuation, and long-term circulatory protection.

6) Clinical Consensus

Cross-disciplinary consensus emphasizes that long-term management of respiratory diseases should not rely solely on pharmacological control but should also incorporate nutritional and lifestyle interventions to reduce systemic inflammatory burden.

Mulberry leaves, through their combined effects on inflammation, oxidative stress, and metabolism, align closely with international nutrition and respiratory consensus. They are particularly suitable for:

- COPD and asthma patients with metabolic syndrome or diabetes;
- Populations exposed to long-term high inflammatory or oxidative stress states (e.g., smoking, pollution);
- Respiratory patients with concomitant cardiovascular risks.

7) Conclusion

Mulberry leaves (*Morus alba*) have transitioned from a traditional botanical to an evidence-based nutritional intervention factor. Their unique value lies in providing systemic “background optimization” through three key axes: metabolic regulation, inflammation and oxidative stress control, and vascular protection.

Current human clinical evidence and international consensus both support its application across diverse respiratory pathologies including acute infections, asthma, COPD, and pulmonary fibrosis. As the core “background noise regulator” in formulations, mulberry leaves synergize with other nutrients to establish multidimensional complementarity.

Altogether, they offer a cross-disciplinary and translational clinical strategy for the comprehensive management of respiratory diseases.