Keyora LungOra 8 in 1

A Clinically Evidenced “Three-Axis, Six-Module Framework” Strategy for Multi-Nutrient Intervention in Respiratory Disorders

Nutritional Pharmacology Targeting Antiviral, Anti-Inflammatory, Antioxidant, and Structural Repair Mechanisms

Abstract

Respiratory diseases - from acute viral infections to asthma, COPD, and fibrosis - share a convergent pathobiology: early failure of antiviral/innate defenses, mid-course amplification via inflammation–oxidative loops, and downstream loss of barrier integrity with inadequate elastic-network repair under a noisy metabolic milieu.
Single-target nutrition rarely closes this loop.

We present a systems nutrition model - the ***Three-Axis, Six-Module Framework*** - operationalized in Keyora LungOra 8 in 1.

- **Axis I (Antiviral & Immune-Regulatory Axis)** integrates *Module I* (antiviral activity + innate immune activation) and *Module II* (regulation of inflammation, inflammasome, and allergic responses).

- **Axis II (Antioxidant–Barrier Homeostasis Axis)** centers on *Module III* (antioxidant defense and barrier maintenance).

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- **Axis III (Ventilation-Structure-Metabolism Axis)** couples *Module IV* (mucociliary dynamics and ventilation improvement), *Module V* (structural repair and elastic-network reconstruction), and *Module VI* (metabolism-inflammation decoupling and systemic noise reduction).

This architecture maps nutrients to specific path nodes and stage-specific roles rather than listing ingredients.

Upstream interception is achieved by **quercetin** (multi-point viral life-cycle blockade and zinc-ionophore action), **zinc** (intracellular RdRp inhibition), and **elderberry** (glycoprotein attachment blockade, RCT-supported symptom reduction), while **vitamin D** induces AMPs and re-balances immune polarity; **vitamin C** prolongs the antiviral chain via redox cycling. Mid-course control layers **bromelain** (mucolysis + inflammatory down-shift) over the antioxidant–barrier scaffold (vitamin C, quercetin, elderberry, zinc, vitamin D). Downstream, **fish cardiac bulb–derived elastin peptides** supply the elastin-specific cross-linking residues (desmosine/isodesmosine) that are otherwise irreplaceable - redirecting repair from collagen-dominant rigid patching toward functional elastic-network regeneration in synergy with vitamin C. **Mulberry leaf (1-DNJ)** attenuates postprandial spikes and the AGE–RAGE axis, lifting the inflammatory activation threshold and dampening systemic “metabolic noise.”
Collectively, this yields a closed intervention chain from invasion and replication control to barrier stabilization, elastic-network reconstruction, and metabolic decoupling.

The framework transforms multi-nutrient support into a stage-aware, node-precise, and synergy-accountable strategy:

- Early antiviral/innate activation with replication blockade;
- Containment of inflammasome/allergic and oxidative amplification while re-establishing mucociliary flow;
- Functional (not merely structural) ECM recovery with durable elastic recoil;
- Background metabolic quieting that stabilizes the whole system.

This constitutes a translational template for stratifying populations and timing interventions across acute care, subacute repair, and chronic maintenance.

Keywords

Acute respiratory infections; Influenza; COVID-19; Asthma; Chronic obstructive pulmonary disease (COPD); Post-viral sequelae; Pulmonary fibrosis; Antiviral defense; Innate immune activation; Inflammasome modulation; Anti-allergic regulation; Antioxidant buffering; Barrier stabilization; Mucociliary clearance; Ventilation improvement; Extracellular-matrix repair; Elastic-network reconstruction; Metabolism-inflammation decoupling; Systemic noise reduction; Viral entry and replication; Cytokine amplification; Oxidative stress; Epithelial/endothelial leak; Mucus hyper-viscosity; Airflow limitation; Loss of pulmonary compliance; Low-quality fibrotic repair; AGE–RAGE–driven inflammation; Metabolic dysregulation; Prolonged recovery trajectory.

Respiratory diseases represent a major global public health challenge, spanning from acute upper respiratory tract infections, influenza, and COVID-19 to chronic conditions such as chronic obstructive pulmonary disease (COPD), asthma, and pulmonary fibrosis. These disorders are consistently characterized by high incidence, frequent recurrence, and long-term clinical burden.

Their pathophysiological basis extends beyond direct pathogen-induced tissue damage to encompass immune dysregulation, cytokine storm-driven inflammation, oxidative stress, epithelial barrier disruption, and impaired tissue repair.
Clinical experience has demonstrated that single-target interventions rarely address the full complexity of these pathways, whereas multi-nutrient strategies - through complementary and synergistic mechanisms across multiple nodes - are emerging as a critical direction in functional respiratory nutrition.

Grounded in clinical evidence, the *Keyora LungOra 8 in 1* framework establishes a “Three-Axis, Six-Module Framework” model, in which the three regulatory axes - immune modulation, antioxidant defense, and structural repair - are further articulated into six mechanistic modules:

- Module I: Antiviral activity and activation of innate immunity
- Module II: Regulation of inflammation, inflammasomes, and allergic responses
- Module III: Antioxidant defense and maintenance of barrier integrity
- Module IV: Mucociliary dynamics and ventilatory improvement

- Module V: Structural repair and elastic network reconstruction
- Module VI: Metabolism–inflammation coupling and systemic "noise reduction"

This framework not only encompasses the entire disease continuum from acute to chronic and convalescent stages, but also provides a systematic integration of multi-nutrient actions into a coherent model of respiratory nutritional pharmacology.

1) Quercetin (1200 mg/day):

Core Multi-Target Agent for Antiviral and Inflammatory Regulation

Quercetin, one of the most extensively studied dietary flavonoids, serves as a central hub in Keyora LungOra 8 in 1, linking the continuum of frontline antiviral defense, mid-phase inflammation control, and downstream homeostatic restoration. Its role is defined by three major dimensions: multi-target antiviral blockade, dual anti-inflammatory and anti-allergic regulation, and systemic intervention in metabolism–inflammation coupling.

1.1) Antiviral activity: multilayer blockade

Quercetin exerts a "multi-point interception" effect across the viral life cycle:

- Pre-entry: inhibits binding of viral glycoproteins to host receptors, reducing invasion efficiency
- Replication: suppresses viral proteases and uncoating, weakening replication chains

- Post-replication: functions as a zinc ionophore, increasing intracellular zinc concentrations and thereby enhancing zinc-mediated inhibition of RNA-dependent RNA polymerase (RdRp)

Outcome: Disruption of multiple viral stages, lowering viral load.

1.2) Anti-inflammatory and anti-allergic regulation

- Inflammasome suppression: down-regulates NLRP3 activation, reducing excessive IL-1β and IL-18 release, thereby preventing cytokine storm
- Fibrosis and allergic modulation: interferes with TGF-β/Smad signaling, limiting fibroblast and mast cell hyper-activation, thus buffering fibrotic and allergic responses

Outcome: Controlled inflammatory amplitude, reduced chronic inflammation and allergic burden.

1.3) Systemic intervention in metabolism–inflammation coupling

In chronic airway disease or post-infectious states, systemic immune-metabolic imbalance is common. Quercetin:

- Activates AMPK and inhibits mTOR, redirecting immune cell metabolism from glycolysis toward mitochondrial oxidation

- Reduces pro-inflammatory M1 macrophages while promoting reparative M2 phenotypes
- Lowers low-grade systemic inflammation and energy expenditure, attenuating systemic “inflammatory noise”

Outcome: Facilitates transition from a “high-inflammation, hypermetabolic” state to a “low-inflammation, reparative homeostasis” state.

Summary: Within Keyora LungOra 8 in 1, quercetin is positioned as a core multi-target agent, simultaneously providing antiviral blockade, inflammatory and allergic modulation, and systemic metabolic stabilization - a pivotal anchor across the entire therapeutic chain.

2) Bromelain (2400 GDU/g, 300 mg/day):

Mucolytic and Anti-Inflammatory Enzyme for Ventilatory Enhancement

Bromelain, a proteolytic enzyme complex with high bioactivity (2400 GDU/g), acts as a dual-action factor in respiratory rehabilitation. It not only directly reduces mucus viscosity and improves airway ventilation, but also attenuates inflammation by suppressing mediators and clearing inflammatory by-products.

2.1) Mucus regulation and ventilation improvement

Excessively viscous sputum obstructs airways and compromises ventilation. Bromelain:

- Degrades mucin cross-linking structures via proteolytic activity, reducing mucus viscosity
- Supports ciliary clearance and improves airflow dynamics
- Achieves clinically relevant thresholds of mucus fluidity, especially in patients with heavy mucus burden

Outcome: Reduced airway resistance and improved ventilatory efficiency.

2.2) Anti-inflammatory mechanisms: limiting amplification

In airway inflammation, pro-inflammatory cytokines and enzymes exacerbate damage. Bromelain:

- Down-regulates COX-2, PGE_2, IL-1β, IL-6, TNF-α
- Up-regulates IL-10, strengthening negative feedback of inflammation
- Indirectly decreases NLRP3 inflammasome activation, mitigating cytokine storm risk

Outcome: Attenuation of local and systemic inflammatory background, creating a low-inflammation environment conducive to repair.

2.3) Systemic modulation and metabolic unloading

- Reduces circulating inflammatory mediators and protease activity, limiting ECM degradation fragments

- Clears inflammatory by-products, easing the burden on hepatic and renal metabolism
- Acts synergistically with quercetin and vitamin C, forming a “signal suppression + by-product clearance” dual anti-inflammatory mode

Outcome: Mitigates metabolism–inflammation coupling and enhances overall respiratory recovery quality.

Summary: Within Keyora LungOra 8 in 1, bromelain functions as a triple-action factor for mucus regulation, inflammation suppression, and ventilation improvement.
By simultaneously improving airway patency and reducing systemic inflammatory load, it emerges as a frontline agent in respiratory rehabilitation.

3) Elderberry (Sambucus nigra) 30:1, 150 mg/day:

Comprehensive Support Factor for Antiviral Defense and Basement Membrane Protection

Elderberry (Sambucus nigra), a plant-derived nutrient widely investigated in respiratory health, is rich in anthocyanins and polyphenols. It exerts multi-target antiviral effects that shorten disease duration while simultaneously alleviating inflammation and oxidative injury. In doing so, it provides full-spectrum protection and repair support across both acute and chronic stages of respiratory disease.

3.1) Multi-target antiviral activity and disease course reduction

- Interferes with viral binding to host cell receptors, reducing invasion
- Inhibits viral replication chains, lowering viral load
- Clinical trials confirm shortened duration of colds and influenza, with relief of cough, fever, and sore throat

Outcome: Weakens viral burden at the frontline and shortens disease duration.

3.2) Anti-inflammatory and antioxidant protection of airways and basement membrane

- Down-regulates the NF-κB pathway, reducing pro-inflammatory mediators such as TNF-α and IL-6
- Anthocyanins act as potent antioxidants, buffering ROS/RNS and protecting ECM and basement membrane proteins (collagen IV, laminin)
- Supports re-adhesion of epithelial and endothelial cells, enhancing the stability of the gas-exchange barrier

Outcome: Provides a “low-inflammation, low-oxidation” background favorable for structural repair.

3.3) Systemic support and buffering of metabolic inflammation

- Restores immune balance, lowering systemic inflammatory noise
- Reinforces the antioxidant network, prolonging the efficacy of quercetin and VC
- Reduces systemic fatigue and chronic inflammatory load

Outcome: Extends benefits from the local respiratory tract to systemic homeostatic support.

Summary: Within Keyora LungOra 8 in 1, elderberry is positioned as a comprehensive support factor: blocking viral entry and shortening disease course in early stages, buffering inflammation and oxidative stress during repair, protecting basement membrane and ECM integrity, and synergizing with other components to reduce systemic inflammation. It acts as a crucial bridge connecting acute defense, chronic alleviation, and systemic support.

4) Fish cardiac bulb–derived elastin peptides, 20 mg/day:

Driving Force for Structural Repair and Pulmonary Function Reconstruction

In both acute and chronic respiratory diseases, the elastic connective tissues of the alveolar walls and broncho-vascular network are among the earliest to be damaged and the most difficult to restore.

Inflammation and oxidative stress lead to elastin fiber rupture, basement membrane collapse, and ECM disorganization. The body often compensates by depositing low-quality collagen in place of elastin, resulting in a form of rigid repair.

Consequently, alveoli lose their natural elasticity, ventilation and gas-exchange efficiency decline, and patients experience long-term loss of respiratory reserve and reduced exercise tolerance.

The unique value of fish cardiac-derived elastin peptides lies in their ability to directly supply the characteristic cross-linking amino acids (desmosine and isodesmosine) essential for elastin fiber repair - raw materials absent from conventional protein or collagen supplementation.

Once incorporated into newly formed elastin fibers, these peptides not only repair structural breaks but also restore the flexibility and compliance of alveolar walls and the broncho-vascular scaffold. With the supportive role of vitamin C, this process enables a transition from mere structural patching to functional reconstruction.

Thus, in the context of respiratory tissue repair, the role of Fish cardiac bulb–derived elastin peptides goes beyond accelerating healing. They guide repair toward the reconstruction of high-quality, physiologically functional elastic networks, thereby improving pulmonary compliance, stabilizing gas exchange, and reducing the long-term risk of fibrosis.

4.1) Providing Essential Raw Materials for Elastin Fiber Reconstruction

In respiratory diseases, the elastic fibers of the alveoli and vascular walls are the structures most vulnerable to inflammation and oxidative stress. Once these fibers rupture or lose their cross-linking amino acids, natural repair often relies on low-quality collagen deposition as a compensatory mechanism.

However, such replacement repair lacks flexibility, leading instead to rigidity and functional loss.

A. Enriched in elastin-specific cross-linking factors

Desmosine and isodesmosine are unique cross-linking amino acids found exclusively in elastin, and they represent the most difficult components of the ECM to regenerate naturally during repair. Their long-term absence is a fundamental reason why alveoli and vascular walls fail to regain their original elasticity. Supplementation with these peptides directly addresses this critical deficiency.

B. Direct integration into newly synthesized elastin fibers

Unlike generic amino acids that require metabolic processing and reassembly, the short peptide chains and cross-linking residues present in fish cardiac bulb-derived elastin peptides can be directly incorporated into nascent elastin fiber networks. This process effectively repairs the ruptures and defects caused by inflammation and oxidative stress, restoring ECM integrity and continuity.

C. Distinction from simple collagen supplementation

Collagen primarily contributes to filling basement membranes and fibrous scaffolds but does not resolve elastin fiber rupture. In contrast, fish cardiac bulb-derived elastin peptides precisely target damaged elastic connective tissues, repairing the flexible matrix of alveolar and vascular walls rather than providing a rigid structural substitute.

D. Outcome: Restoration of both structure and function

With vitamin C–mediated hydroxylation and cross-linking support, the newly synthesized ECM achieves not only structural reconstruction but also flexibility and extensibility. This allows alveoli to expand and recoil effectively, while vascular walls regain compliance - together enhancing pulmonary ventilation and gas-exchange efficiency.

4.2) Deep-Level Repair: Reconstruction from Structure to Function

In the trajectory of respiratory injury and recovery, the decisive factor for long-term prognosis is not merely the resolution of inflammation or symptomatic relief, but rather the ability of pulmonary elastic connective tissues to undergo high-quality repair.
If recovery remains confined to symptom control without restoration of ECM flexibility and functionality, progressive loss of respiratory reserve and long-term pulmonary capacity is inevitable.

A. Structural dimension: precise repair of ruptures and defects

Inflammation and oxidative stress disrupt the pulmonary microarchitecture by inducing elastin fiber rupture, basement membrane damage, and ECM network breakdown. Conventional reparative processes dominated by low-quality collagen deposition may temporarily bridge structural gaps but lack elasticity, ultimately leading to rigidity and heightened fibrosis risk.
The distinct advantage of fish cardiac bulb-derived elastin peptides lies in their enrichment with desmosine and isodesmosine, cross-linking amino acids unique to

elastin.

Upon supplementation, these residues are directly integrated into newly formed elastin fibers, enabling targeted repair of ruptures and defects and restoring ECM continuity and integrity.

B. Functional dimension: transition from rigid repair to flexible regeneration

Collagen-based replacement repair provides structural filling but fails to impart the elasticity required by alveolar walls and vascular structures, resulting in what is termed “rigid repair.” This leads to alveoli that cannot expand adequately and vascular walls with diminished compliance.

Through the provision of cross-linking substrates, and under the hydroxylation and cross-linking facilitation of vitamin C, fish cardiac bulb-derived elastin peptides drive ECM remodeling toward high-quality elastic network reconstruction.

The regenerated alveoli regain the capacity for physiological expansion and recoil, while vascular walls recover compliance, marking a shift from mere structural repair to functional restoration.

C. Clinical significance: from substitute healing to genuine reconstruction

The implications of such “deep repair” extend beyond structural replacement to the achievement of true functional recovery:

- Alveolar ventilation and gas-exchange efficiency are markedly improved, enhancing oxygenation capacity
- Airway resistance is reduced, respiratory workload declines, and exercise tolerance increases
- High-quality elastin repair limits pathological collagen deposition, mitigating long-term risks of fibrosis and irreversible damage

D. Value positioning

Within Keyora LungOra 8 in 1, fish cardiac bulb-derived elastin peptides can be regarded as a core of the core component. By enabling direct ECM-targeted repair, they achieve a closed-loop restoration from structural rebuilding to functional recovery, establishing an irreplaceable foundation for the long-term rehabilitation of both acute and chronic respiratory disorders.

4.3) Synergy with Vitamin C to Enhance Cross-Linking Stability

The reconstruction of elastic fibers requires not only the provision of raw materials but also a stable and precise cross-linking process. Vitamin C plays a pivotal catalytic role in this step: it serves as an essential cofactor for the hydroxylation of proline and lysine, driving the formation of hydroxyproline and hydroxylysine. These hydroxylated residues are prerequisites for stable cross-linking in collagen and elastin and represent the chemical foundation for building a resilient, tensile, and elastic ECM network.

Against this background, fish cardiac bulb-derived elastin peptides provide the cross-linking substrates required for repair. Their enrichment in desmosine and isodesmosine enables direct incorporation into the ECM regenerative pathway, functioning as anchoring sites and structural scaffolds of the elastin fiber network. Through synergistic interaction with hydroxylated amino acids generated under the action of vitamin C, elastin peptides are not merely passively integrated but instead achieve high-quality cross-linking and functional incorporation.

- Stability: abundant and firm cross-linking points reduce the risk of fiber rupture
- Functionality: the reconstructed ECM regains native flexibility and extensibility rather than forming rigid substitutes
- Durability: the regenerated elastic network sustains long-term compliance of airways and alveoli, protecting against inflammatory and oxidative damage

Ultimately, this synergistic repair mode avoids the “rigid repair” associated with low-quality collagen deposition and instead achieves genuine functional reconstruction. Alveoli regain their physiological capacity for expansion and recoil during respiration, vascular walls restore compliance, and gas-exchange efficiency improves - providing a reliable foundation for long-term respiratory rehabilitation.

4.4) Restoring Compliance of Alveoli and Vascular Walls

Normal respiratory function relies on the compliance of alveolar and vascular walls, which determines whether the gas-exchange interface can adequately expand and recoil in response to pressure changes during breathing.

Inflammation, oxidative stress, and ECM injury disrupt elastin fibers, leaving alveoli stiff and vascular walls rigid - directly resulting in insufficient ventilation, reduced gas-exchange efficiency, and increased pulmonary vascular resistance.

A. Recovery of alveolar function

Following ECM repair and elastic network reconstruction, alveolar walls regain the capacity to expand and recoil. During inspiration, alveoli can fully expand, increasing the surface area for gas exchange; during expiration, they contract smoothly, minimizing air trapping. This dynamic process markedly improves alveolar ventilation and diffusion efficiency.

B. Enhanced vascular wall flexibility

Through the synergistic repair of vascular elastic connective tissue by elastin peptides and vitamin C, vascular walls recover their flexibility under pressure fluctuations.

As a result, pulmonary vascular resistance decreases, pulmonary blood flow distribution becomes more balanced, and both oxygenation capacity and overall hemodynamics improve.

C. Clinical significance during disease course

In conditions such as asthma, COPD, and post-ARDS sequelae, loss of elasticity is a central mechanism driving long-term functional impairment.

High-quality elastin fiber repair not only alleviates acute symptoms but also prevents progressive alveolar stiffening and gas-exchange restriction during recovery. This supports the restoration of exercise tolerance and overall quality of life.

Outcome: By incorporating fish cardiac elastin peptides, ECM repair advances beyond structural replacement to achieve functional reconstruction of pulmonary elastic connective tissue - truly restoring the compliance of alveoli and vascular walls and laying the foundation for long-term respiratory health.

4.5) Reducing the Risk of Fibrosis and Long-Term Damage

In the context of acute injury or chronic inflammation, the respiratory system often defaults to abnormal collagen deposition as a compensatory repair mechanism. However, this form of “rigid repair” fails to restore the function of elastic connective tissues. Instead, it results in thickened alveolar walls, vascular stiffening, and loss of compliance, accelerating both the decline of respiratory reserve and the progression of fibrosis.

A. Limiting abnormal collagen deposition

By providing elastin-specific cross-linking factors such as desmosine and isodesmosine, fish cardiac bulb-derived elastin peptides direct the repair process toward true elastin

fiber regeneration rather than simple collagen filling. As a result, the ECM regains flexibility and extensibility, fundamentally reducing the occurrence of rigid repair.

B. Buffering chronic inflammation and oxidative stress

Under persistent inflammatory and oxidative conditions, repair is typically skewed toward fibrosis. The synergy of fish cardiac bulb-derived elastin peptides with vitamin C not only improves ECM regeneration quality but also fosters an anti-inflammatory and antioxidant environment. This attenuates fibroblast overactivation and TGF-β–related signaling, thereby lowering fibrotic progression.

C. Preserving ECM flexibility

The regenerated ECM retains physiological elasticity, allowing alveoli and vascular walls to maintain compliance over the long term. This functional flexibility is critical to preventing ongoing respiratory decline and ensures sustained efficiency in gas exchange and pulmonary hemodynamics.

D. Clinical significance

For patients with COPD, post-ARDS sequelae, or interstitial lung diseases at risk of fibrosis, the integration of fish cardiac bulb-derived elastin peptides offers more than short-term respiratory improvement.

By slowing fibrotic progression and preventing irreversible damage, these peptides

contribute to genuine long-term functional recovery, preserving pulmonary reserve and supporting greater capacity for daily activity and exercise.

Outcome: Through a combination of high-quality elastin regeneration and optimization of the anti-inflammatory/antioxidant environment, fish cardiac bulb-derived elastin peptides help the respiratory system avoid the “fibrosis trap” and achieve the triple goal of structural repair, functional restoration, and long-term stability.

Summary: Within *Keyora LungOra 8 in 1*, fish cardiac bulb-derived elastin peptides are positioned as the driving force of repair. They not only supply the essential substrates for ECM regeneration but also, in synergy with vitamin C, ensure that repair leads to flexible, functional reconstruction.

Their core value lies in the deep repair of damaged pulmonary elastic connective tissues - restoring the mechanical performance of alveoli and vascular walls, improving ventilation and gas exchange efficiency, and establishing a dual foundation of structural and functional recovery for long-term rehabilitation.

5) Mulberry Leaf Extract (30:1) 90 mg/day:

Systemic Support Factor for Metabolic Regulation and Inflammatory Noise Buffering

Traditionally valued for its role in “clearing the lungs and moistening dryness,” mulberry leaf (Morus alba) has been shown in modern studies to be rich in 1-deoxynojirimycin

(DNJ), flavonoids, and polyphenols. These compounds significantly inhibit α-glucosidase activity, thereby reducing postprandial glucose spikes.

By buffering blood glucose fluctuations and suppressing the formation of advanced glycation end-products (AGEs), mulberry leaf acts not as a frontline factor in respiratory nutritional intervention but rather as a background regulator, responsible for metabolic modulation, inflammatory buffering, and systemic “noise reduction.”
Its inclusion extends the logic of LungOra 8 in 1 from localized airway protection to the maintenance of systemic metabolic homeostasis, filling a critical gap in holistic defense.

5.1) Postprandial glucose regulation

- DNJ competitively inhibits α-glucosidase, delaying carbohydrate breakdown
- Reduces postprandial glucose peaks and lowers the burden of excessive insulin secretion
- Stabilizes glycemic curves, preventing metabolic stress under inflammatory conditions

Outcome: Weakens the coupling between hyperglycemia and systemic inflammation.

5.2) Mitigation of glycation stress and AGE burden

- Hyperglycemia accelerates AGE formation, aggravating ECM stiffening and amplifying inflammation

- Mulberry polyphenols suppress AGE formation and reduce binding to RAGE receptors
- Decreases glycation-driven oxidative and inflammatory signaling at the source

Outcome: Provides a “low-glycation background” that supports ECM repair and systemic homeostasis.

5.3) 5.3) Anti-inflammatory and antioxidant support

- Mulberry flavonoids reduce TNF-α and IL-6, alleviating chronic low-grade inflammation
- Suppress lipid peroxidation and free radical chain reactions
- Act synergistically with quercetin, elderberry, and vitamin C to strengthen the anti-inflammatory and antioxidant network

Outcome: Further reduces systemic inflammatory noise.

5.4) 5.4) Systemic clinical relevance

- Metabolic syndrome or diabetic patients: buffers glycemic fluctuations and lowers the risk of metabolism–inflammation interplay
- Respiratory disease patients with metabolic imbalance: improves rehabilitation quality and reduces risk of chronic exacerbation

- Elderly populations: provides “metabolic protection,” reducing the combined impact of inflammaging and respiratory decline

Summary: Within Keyora LungOra 8 in 1, mulberry leaf extract is positioned as a metabolism–inflammation background regulator.

Rather than directly contributing to antiviral defense or structural repair, it supports respiratory recovery through the cascade of postprandial glucose suppression → reduced glycation stress → alleviated metabolic inflammatory noise.

This component completes the framework of Keyora LungOra 8 in 1, transforming it from a localized defense strategy into a closed-loop system of systemic homeostasis.

6) Vitamin D 20 mcg (800 IU)/day:

Core Regulatory Factor for Immune Polarity and Barrier Homeostasis

The role of vitamin D in respiratory health has been extensively validated in both clinical and experimental studies. Through the vitamin D receptor (VDR), it directly modulates innate and adaptive immune polarity - inducing antimicrobial peptides (e.g., LL-37, β-defensins) to strengthen frontline defense, while simultaneously enhancing Treg activity and suppressing Th17-driven inflammatory amplification.

In parallel, vitamin D supports epithelial and endothelial barrier integrity, acting synergistically with zinc to maintain tight junction protein expression.

Accordingly, vitamin D is positioned within Keyora LungOra 8 in 1 as a central factor for immune and barrier homeostasis, ensuring smooth transition from acute defense to long-term repair.

6.1) VDR–antimicrobial peptide axis: strengthening innate immune defense

- VDR activation induces secretion of antimicrobial peptides such as LL-37 and β-defensins
- Enhances the ability of airway epithelial cells to resist viral and bacterial invasion
- Reduces risk of secondary infections, particularly in immunocompromised or elderly populations

Outcome: Reinforces the first-line defense of the respiratory epithelium.

6.2) Immune polarity recalibration: reducing inflammatory amplification

- Enhances Treg cell function and suppresses excessive Th17/Th1 responses
- Down-regulates NF-κB and JAK/STAT signaling, lowering TNF-α, IL-6, and IL-17 levels
- Reduces the high-energy inflammatory mode of the immune system, restoring balance

Outcome: Prevents cytokine storms and mitigates chronic inflammatory background.

6.3) Barrier homeostasis support

- Promotes expression of tight junction proteins including occludin, claudin, and ZO-1
- Works synergistically with zinc to repair epithelial and endothelial integrity
- Decreases leakage, mediator spillover, and barrier dysfunction

Outcome: Maintains barrier stability and improves alveolar–vascular exchange efficiency.

6.4) Anti-fibrotic effects

- Inhibits TGF-β/Smad signaling, limiting fibroblast activation
- Prevents abnormal ECM deposition and rigid repair
- Acts synergistically with quercetin and fish cardiac bulb-derived elastin peptides to ensure repair quality

Outcome: Reduces risk of fibrosis and enables long-term functional recovery.

Summary: Within Keyora LungOra 8 in 1, vitamin D functions as the core regulator of immune and barrier homeostasis. By integrating antimicrobial peptide induction, immune polarity recalibration, barrier restoration, and anti-fibrotic effects, it bridges acute defense with chronic recovery within the *Three-Axis, Six-Module Framework*.

In synergy with zinc, quercetin, and vitamin C, vitamin D ensures that the intervention system not only provides antiviral and anti-inflammatory benefits but also sustains long-term structural and metabolic stability.

7) Vitamin C 90 mg/day:

Antioxidant Core and Catalytic Factor for ECM Repair

Vitamin C is one of the most classical agents in respiratory nutritional intervention. Beyond being a water-soluble antioxidant that scavenges free radicals and mitigates oxidative stress during infection and inflammation, it is also an essential cofactor for collagen and elastin synthesis, ensuring stable cross-linking and functional ECM regeneration. In addition, vitamin C regenerates quercetin and elderberry polyphenols, extending the activity of the antioxidant network.
Thus, it provides oxidative buffering in the acute phase and ensures structural quality during the repair phase.

Within Keyora LungOra 8 in 1, vitamin C is positioned as the “antioxidant hub and guardian of repair quality.”

7.1) Antioxidant core

- Directly scavenges ROS/RNS, buffering oxidative stress in acute phases
- Regenerates quercetin and elderberry anthocyanins, sustaining the antioxidant cycle
- Protects cell membranes and DNA, reducing pro-inflammatory signaling

Outcome: Establishes a complementary “aqueous–lipid phase” antioxidant network.

7.2) Catalytic factor for ECM repair

- Serves as an essential cofactor for proline and lysine hydroxylases, enabling collagen and elastin hydroxylation
- Ensures triple-helix integrity and cross-linking stability of newly synthesized ECM
- Works synergistically with fish cardiac bulb-derived elastin peptides to promote functional elastin fiber regeneration

Outcome: Achieves flexible reconstruction rather than rigid repair.

7.3) Anti-inflammatory and anti-fibrotic support

- Suppresses NF-κB activation, reducing IL-6 and TNF-α
- Inhibits TGF-β/Smad signaling, limiting aberrant fibroblast activation
- Under chronic conditions, prevents abnormal ECM deposition and fibrotic progression

Outcome: Mitigates long-term functional decline and preserves respiratory compliance.

Summary: Within Keyora LungOra 8 in 1, vitamin C acts as both an acute-phase oxidative buffer and a repair-phase catalytic safeguard. It not only counters oxidative and inflammatory surges in early stages but also ensures ECM repair quality in later stages. Through synergy with quercetin, elderberry, and fish cardiac elastin peptides, vitamin C bridges antioxidant defense, anti-inflammatory support, and structural regeneration across different stages of recovery.

8) Zinc 15 mg/day:

Synergistic Cofactor for Antiviral Replication Control and Immune Homeostasis

Zinc is an indispensable trace element for immune and barrier function in the respiratory system. It plays essential roles in antiviral defense, maintenance of immune cell activity, and regulation of barrier protein expression.

Importantly, zinc works in synergy with quercetin through a unique ionophore mechanism, which enables zinc to efficiently enter cells and directly inhibit RNA-dependent RNA polymerase (RdRp), thereby blocking viral replication.

At the same time, zinc supports tight junction integrity and epithelial repair, contributing to barrier stability and buffering chronic inflammation.

Within Keyora LungOra 8 in 1, zinc is positioned as a synergistic pivot for antiviral defense and immune balance.

8.1) Inhibition of viral replication

- Directly suppresses RdRp activity, disrupting viral RNA replication
- Increases intracellular zinc concentrations when combined with ionophores such as quercetin
- Blocks viral replication chains, improving antiviral efficiency

Outcome: Direct molecular-level reduction of viral amplification speed.

8.2) Immune support and homeostatic regulation

- Sustains NK cell and T cell functions, enhancing immune clearance capacity
- Down-regulates NF-κB signaling, reducing inflammatory mediators such as IL-6 and TNF-α
- Prevents immune overactivation and promotes return to balanced immune responses

Outcome: Achieves the dual balance of effective antiviral activity with avoidance of inflammatory excess.

8.3) Barrier and antioxidant support

- Promotes expression of tight junction proteins such as occludin, claudin, and ZO-1
- Maintains the integrity of respiratory epithelium and vascular endothelium, reducing leakage
- Serves as a required cofactor for superoxide dismutase (SOD), facilitating ROS clearance

Outcome: Protects barrier function and reduces oxidative stress burden.

Summary: In Keyora LungOra 8 in 1, zinc is positioned as a synergistic factor for antiviral replication control, immune balance, and barrier protection. Through its ionophore-based partnership with quercetin, zinc precisely blocks viral replication while sustaining immune

and barrier stability. In addition, as part of the antioxidant network, it establishes a vital link between frontline antiviral defense and downstream barrier homeostasis.

9) Conclusion

The design of Keyora LungOra 8 in 1 is grounded in *the Three-Axis, Six-Module system-based intervention framework*, enabling precise alignment of nutritional factors with the distinct pathological stages of respiratory diseases.

While each of the eight ingredients addresses specific mechanisms, their complementary and synergistic actions form a continuous chain of intervention spanning frontline defense → mid-phase buffering → downstream repair and systemic homeostasis.

- Bromelain: Delivers a triple effect on mucus-inflammation-ventilation through potent proteolytic activity, directly improving airway patency and reducing the burden of inflammatory by-products.
- Quercetin: Functions as the central hub with multi-target antiviral blockade, regulation of inflammation and allergic responses, and modulation of metabolism–inflammation coupling.
- Elderberry: Provides anthocyanin- and polyphenol-based antiviral, anti-inflammatory, antioxidant, and basement membrane protection, while extending systemic buffering support - serving as a bridge from acute defense to chronic support.

- Vitamin C: Acts as the aqueous-phase antioxidant core, mitigating oxidative stress, catalyzing high-quality ECM repair, and regenerating other antioxidants such as quercetin - ensuring sustained operation of the antioxidant network.
- Vitamin D: Through the VDR–antimicrobial peptide axis, immune polarity recalibration, and barrier homeostasis, it provides central regulation between acute defense and long-term repair, reducing immune imbalance and fibrotic risk.
- Zinc: Combines antiviral replication inhibition, immune support, and barrier stabilization. In synergy with quercetin as a zinc ionophore, it maximizes antiviral effects while sustaining immune and antioxidant foundations.
- Fish cardiac elastin peptides: Supply critical substrates for ECM regeneration and, in synergy with vitamin C, ensure that repair progresses toward functional elastic network reconstruction. Their core value lies in deep repair of damaged pulmonary connective tissues - restoring alveolar and vascular mechanics, ventilation efficiency, and gas-exchange capacity.
- Mulberry leaf extract: By inhibiting postprandial hyperglycemia and glycation stress, it buffers metabolism–inflammation noise, particularly benefiting metabolically vulnerable populations and providing systemic stability.

Together, these eight core components form an intervention system that is complementary, progressive, and synergistic:

- Frontline (bromelain, quercetin, elderberry, zinc) → antiviral defense, anti-inflammatory action, and ventilation improvement
- Mid-phase (vitamin C, vitamin D) → antioxidant defense, barrier stability, and immune modulation
- Downstream (fish elastin peptides, mulberry leaf extract) → structural repair and metabolic buffering

In summary, Keyora LungOra 8 in 1 achieves full-spectrum coverage through multi-axis, multi-module, and multi-nutrient synergy - addressing pathogen interception, inflammation control, oxidative protection, ventilation enhancement, tissue repair, and metabolic noise reduction.

This evidence-based formulation not only demonstrates theoretical integrity within nutritional pharmacology but also gains support from clinical evidence, offering a novel academic framework and practical pathway for nutritional intervention in respiratory disorders.

Comprehensive Mechanistic Framework of the *"Three-Axis, Six-Module"* Multi-Nutrient Intervention for Respiratory Health

From Immune Defense to Structural Repair: A Systematic Analysis of Regulatory Pathways

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The maintenance of respiratory health does not rely on a single pathological pathway but results from the interplay of multiple mechanisms including immune defense, inflammation control, oxidative stress regulation, and structural tissue repair.

Evidence indicates that whether triggered by acute infections leading to respiratory symptoms, or by long-term damage such as chronic obstructive pulmonary disease (COPD) and fibrosis, the shared hallmark is multi-axis imbalance:

- Upstream: insufficient antiviral and immune responses allow pathogens to gain a replication advantage in early stages
- Midstream: excessive amplification of inflammation and oxidative stress exacerbates mucosal and alveolar injury
- Downstream: limited repair of barrier structures and elastic networks promotes recurrence and chronic progression

Thus, nutritional intervention for respiratory diseases must move beyond single-nutrient or single-mechanism strategies. Instead, it should be based on multi-axis synergy - acting early at the stage of pathogen invasion, controlling amplification loops of inflammation and oxidative stress, while simultaneously supporting structural rebuilding and functional recovery.

Keyora LungOra 8 in 1 is designed upon this logic, constructing three major regulatory axes - immune defense, inflammatory control, and barrier/structural repair - which are further refined into ***six key modules:***

- Module I: Antiviral activity and activation of innate immunity
- Module II: Regulation of inflammation, inflammasomes, and allergic responses
- Module III: Antioxidant defense and maintenance of barrier integrity
- Module IV: Mucociliary dynamics and improvement of ventilation
- Module V: Structural repair and reconstruction of elastic networks
- Module VI: Metabolism-inflammation coupling and systemic noise reduction

This Three-Axis, Six-Module framework not only provides a systematic theoretical foundation for nutritional intervention but also establishes the basis for stratified strategies across different clinical stages and population types.

I Regulatory Axis I - Antiviral Immune Defense

In the course of respiratory diseases, pathogen invasion and the host’s antiviral defense represent the earliest stage of activation.

Whether triggered by influenza viruses, coronaviruses, or other respiratory RNA viruses, the pathogenic process is commonly characterized by barrier penetration, rapid replication, and immune evasion.

If innate immunity is insufficient, the virus can rapidly disseminate, leading to heightened inflammation and secondary tissue injury.

Thus, the strength of early antiviral activity and innate immune activation largely determines both disease severity and recovery trajectory.

Nutritional pharmacology studies have shown that a variety of natural bioactive compounds and essential trace elements can reinforce antiviral defense through distinct mechanisms:

- Quercetin employs a *multi-point interception* strategy—blocking viral entry, inhibiting uncoating and protease activity, and acting as a zinc ionophore to amplify antiviral effects.
- Bromelain degrades airway mucin proteins, reducing viral retention and aggregation on respiratory surfaces, while simultaneously alleviating local inflammation to limit viral entry and spread.
- Fish cardiac bulb-derived elastin peptides support basement membrane and ECM integrity, decreasing the likelihood of viral barrier penetration while supplying substrates for subsequent repair.
- Elderberry anthocyanins and polyphenols bind viral glycoproteins, blocking attachment, with clinical trials demonstrating reduced duration and severity of cold and influenza symptoms.
- Mulberry leaf extract lowers postprandial hyperglycemia and glycation stress, attenuating metabolism–inflammation coupling and providing a more stable systemic background for antiviral immunity.

- Vitamin C functions during acute infection as a water-phase antioxidant, clearing virus-induced ROS, reducing cellular damage, and regenerating quercetin and elderberry polyphenols to extend the antiviral effect chain.
- Vitamin D, via VDR signaling, induces antimicrobial peptides (LL-37, β-defensins), thereby strengthening mucosal innate immunity while balancing immune polarity.
- Zinc directly inhibits RNA-dependent RNA polymerase (RdRp), blocking viral replication chains, and supports T cell and NK cell activity.

Within the *Keyora LungOra 8 in 1* immune-antiviral axis, these eight components act in complementary synergy:

- Upstream: elderberry and quercetin block viral entry
- Midstream: zinc and quercetin suppress replication, while vitamin C prolongs antiviral activity
- Downstream: vitamin D sustains immune polarity and barrier stability, bromelain improves the mucosal environment, fish cardiac bulb-derived elastin peptides reinforce barrier structure, and mulberry leaf reduces metabolic “noise”

This multi-nutrient intervention strategy covers the entire cascade - from viral invasion and replication to host immune balance and barrier defense.

It not only reduces viral replication rates in the early stages but also alleviates oxidative stress and inflammatory amplification, laying a robust foundation for the four downstream

regulatory dimensions: inflammation control, barrier homeostasis, structural repair, and systemic noise reduction.

1) Module I - Antiviral and Innate Immune Activation

The pathogenic course of respiratory viruses generally proceeds through three stages: attachment and entry, endocytosis and uncoating, and replication and dissemination. When epithelial cells encounter viral particles, they activate innate immune defenses, including recognition by pattern recognition receptors (PRRs), release of interferons (IFNs), and secretion of antimicrobial peptides (AMPs).
The efficiency of this initial response directly determines the pace of viral replication and spread, as well as the intensity of subsequent inflammatory reactions.

Accordingly, nutritional interventions that strengthen barrier defenses, inhibit replication, and activate innate immunity during this early stage can decisively shape both the severity and the duration of disease.

1.1) The multi-point interception mechanism of quercetin

Quercetin, a flavonoid repeatedly validated in antiviral research on respiratory diseases, demonstrates a multi-point interception capacity. This ability to intervene at multiple stages of the viral life cycle establishes a comprehensive protective chain spanning from entry blockade to replication suppression.

A. Upstream blockade: interference with viral entry

The first step of viral infection involves binding of viral surface glycoproteins to host cell receptors - for instance, influenza hemagglutinin (HA) binding to sialic acid residues, or coronavirus spike protein (S protein) binding to ACE2.

Quercetin can interact with these glycoproteins or their key domains, altering conformations or reducing binding affinity, thereby preventing viral attachment and endocytosis.

This functions as a “frontline defense at the gate,” preventing efficient viral entry and lowering infection probability.

B. Midstream inhibition: weakening viral replication

Even when viruses succeed in entering host cells, quercetin interferes at the replication stage. It inhibits viral proteases - such as influenza PA/PB1 and coronavirus 3CLpro/PLpro - disrupting genome transcription and protein processing.

In parallel, it hampers viral uncoating, restricting the release of viral RNA into the cytoplasm and delaying replication initiation.

This mechanism acts like “cutting the supply line in the factory,” slowing and reducing the scale of viral production.

C. Downstream synergy: zinc ionophore effect

Quercetin has also been identified as a zinc ionophore, facilitating intracellular transport of zinc (Zn^{2+}). Since zinc directly inhibits RNA-dependent RNA polymerase (RdRp), blocking viral RNA synthesis, quercetin indirectly amplifies this effect by raising intracellular zinc concentrations.

This serves as a “biological accelerator,” enabling zinc’s antiviral potency to be fully expressed within cells. Compared with zinc alone, the quercetin–zinc combination exerts markedly stronger suppression of viral replication.

D. Integrated mechanistic significance

Through this multi-point interception model, quercetin operates across the entire viral cycle:

- Upstream: raises the threshold for successful viral entry
- Midstream: weakens replication efficiency and slows viral spread
- Downstream: amplifies zinc-mediated replication inhibition

As a result, quercetin provides both direct antiviral activity and indirect enhancement via zinc synergy. This dual property is particularly critical in the early stages of acute respiratory infection, where rapid intervention can curb viral expansion before large-scale replication and dissemination occur.

1.2) Early Antiviral Supportive Role of Bromelain

Bromelain, a high-activity proteolytic enzyme complex derived from pineapple stems (2400 GDU/g), does not act by directly killing viruses. Instead, it contributes to respiratory infection defense by modifying the airway microenvironment, buffering inflammatory responses, and clearing by-products, thereby indirectly reducing viral invasion and dissemination efficiency.

Within the logic of Module I, bromelain occupies a distinctive role of “upstream clearance, midstream inflammation reduction, and downstream relief.”

A. Upstream clearance: reducing opportunities for viral attachment

During respiratory infections, inflammation often increases mucus secretion and viscosity, turning the airway into a reservoir for viral retention and aggregation.

- Bromelain hydrolyzes mucin cross-linking structures, markedly lowering mucus viscosity
- Enhances ciliary clearance, facilitating expulsion of airway secretions
- As a result, viral residence time and attachment probability on the epithelial surface are significantly reduced

This function acts like “clearing the corridor,” making it harder for pathogens to linger and reducing infection pressure from the outset.

B. Midstream inflammation reduction: weakening the replication environment

Viral replication is often fueled by the pro-inflammatory milieu, where cytokines and tissue proteases disrupt barriers and promote spread.

- Bromelain down-regulates pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, PGE_2, and COX-2
- Simultaneously up-regulates IL-10 and other anti-inflammatory mediators, providing negative feedback
- By lowering the inflammatory background, it indirectly reduces the “fuel supply” that supports viral replication and trans-barrier spread

This process is akin to “turning down the factory heat,” preventing viruses from operating replication machinery at full capacity.

C. Downstream relief: buffering systemic inflammation and barrier injury

Under the dual stress of viral infection and inflammation, numerous ECM degradation fragments and inflammatory by-products enter circulation, amplifying systemic inflammation.

- Bromelain helps clear these fragments through proteolysis, lowering systemic inflammatory “noise”
- Reduces metabolic organ burden, preventing excessive diversion of immune resources

- Creates a low-inflammation environment conducive to barrier repair and immune recalibration

This step acts as a “background cleanup,” preventing local infection from escalating into systemic inflammatory storms.

D. Synergistic significance

Within the Module I chain, bromelain provides a unique environmental regulatory role:

- Upstream → complements elderberry and quercetin as a dual “blockade + clearance” defense
- Midstream → synergizes with quercetin, zinc, and vitamin C to limit replication-supportive inflammatory amplification
- Downstream → prepares a buffered environment for vitamin D and fish cardiac bulb-derived elastin peptides to sustain barrier stability and repair

Thus, in the Regulatory Axis I: Antiviral Immune Defense, bromelain does not act as a direct antiviral combatant but as an environmental modulator.

By ensuring smoother coordination across upstream, midstream, and downstream processes, it slows viral dissemination and reduces the risk of inflammatory escalation.

1.3) Barrier Defense Role of Fish Cardiac-Derived Elastin Peptides

Fish cardiac bulb–derived elastin peptides are small elastin fragments enriched in desmosine and isodesmosine, characteristic cross-linking amino acids that can be efficiently absorbed and directly incorporated into extracellular matrix (ECM) and basement membrane repair. In the early stages of viral infection, the integrity of these structural barriers largely determines whether viruses can penetrate the mucosal and vascular layers to reach deeper tissues. Within the logic of Module I, elastin peptides serve the unique role of “fortifying frontline barriers and reducing invasion efficiency.”

A. Upstream fortification: blocking trans-barrier viral entry

- Following viral attachment, the critical step is penetration of the epithelial barrier into host cells.
- Elastin peptides act as substrates for elastin synthesis and cross-linking, accelerating ECM reinforcement.
- In synergy with vitamin C, newly synthesized elastin fibers achieve higher-quality cross-link stability, strengthening the basement membrane.

Result: even if viral attachment occurs, the likelihood of successful trans-barrier invasion is markedly reduced.

B. Midstream buffering: limiting conditions for replication and spread

- Inflammation and oxidative stress compromise basement membranes, facilitating viral spread to neighboring cells.

- Elastin peptides repair ECM gaps, narrowing viral pathways across intercellular spaces.
- By maintaining tissue flexibility, they help preserve epithelial functional integrity during infection.

Result: viral replication and spread are restricted to localized zones, preventing large-scale dissemination.

C. Downstream synergy: providing a structural basis for immune regulation

- Innate immune responses without stable barriers often trigger excessive inflammation.
- By preserving basement membrane integrity, elastin peptides reduce leakage and spread of inflammatory mediators.
- This minimizes the risk of cytokine storm while creating a stable environment for vitamin D-mediated immune polarity regulation and for zinc and quercetin to exert antiviral replication blockade.

Result: inflammatory amplitude is reduced, and immune interventions become more effective.

E. Synergistic significance

Within Module I, the value of elastin peptides lies in multi-level coordination:

- With bromelain → the former clears mucus obstacles, the latter reinforces deeper barriers
- With vitamin C → supplies ECM repair substrates plus catalyzes cross-linking for a high-quality defense network
- With vitamin D, zinc, and quercetin → maximizes immune and antiviral effects in the context of structural integrity

Thus, in the Regulatory Axis I: Antiviral Immune Defense, fish cardiac–derived elastin peptides act not as direct viral antagonists but as barrier guardians.

Their significance lies in *lowering invasion efficiency, restricting pathways of viral spread, and reducing inflammatory leakage*, thereby providing a robust structural foundation for the entire antiviral defense chain.

1.4) Antiviral Mechanisms of Elderberry

Elderberry has long been used as a traditional botanical remedy and is now widely studied in nutritional immunology, particularly for its role in preventing and managing respiratory infections. Its key bioactive constituents - anthocyanins, flavonoids, and polyphenols - act across multiple stages of the viral life cycle.

A. Blocking viral attachment

Studies demonstrate that elderberry extracts can bind to influenza hemagglutinin (HA) and coronavirus spike protein (S protein), thereby interfering with their interaction with

host receptors. This competitive blockade significantly reduces viral adhesion and entry, functioning as a biochemical shield at the initial “entry gate.”

B. Inhibiting viral replication

In vitro experiments show that elderberry polyphenols suppress viral replication within host cells, evidenced by reduced viral RNA levels and lower viral particle production. Some studies suggest this effect is mediated through modulation of host signaling pathways such as NF-κB and MAPK, which weakens the intracellular environment required for viral replication.

C. Modulating immunity and inflammation

Elderberry exerts both direct antiviral effects and indirect benefits via immune regulation:

- In the early phase, it stimulates moderate release of cytokines (e.g., IL-6, IL-8, TNF-α), facilitating rapid immune activation
- In later phases, its polyphenols reduce excessive inflammation, preventing cytokine storm development

This “early activation, later balance” biphasic immunomodulatory pattern positions elderberry as both an antiviral and anti-inflammatory agent in acute respiratory infections.

D. Clinical evidence

Multiple randomized controlled trials and meta-analyses have demonstrated that elderberry extract can significantly shorten the duration of influenza and acute respiratory infections (typically by 1-2 days) and alleviate symptoms such as fever, sore throat, cough, and nasal congestion. These findings provide solid evidence for its use in acute infection phases and establish its place in respiratory nutritional intervention.

E. Synergistic significance

Elderberry complements other nutrients within the Regulatory Axis I defense chain:

- With quercetin: both block viral entry, but quercetin extends activity into replication and downstream pathways, creating a continuous defense timeline
- With zinc: elderberry reduces early viral burden, while zinc further blocks replication, limiting viral breakthrough
- With vitamin D: elderberry enhances mucosal frontline defense, whereas vitamin D, through antimicrobial peptides and immune polarity regulation, sustains long-term barrier stability

Overall, elderberry’s value lies not only in shortening disease duration, but also in securing a broader intervention window for subsequent anti-inflammatory, antioxidant, and tissue repair processes.

1.5) Mulberry Leaf: Metabolic Homeostasis and Antiviral Support

Mulberry leaf is rich in 1-deoxynojirimycin (1-DNJ), polyphenols, and flavonoids, with its primary pharmacological value lying in α-glucosidase inhibition. This slows carbohydrate breakdown and absorption, thereby blunting postprandial glycemic spikes.

During the early phase of viral infection, metabolic status is tightly linked to immune competence: hyperglycemia and glycation stress not only impair innate immunity but also amplify inflammatory responses.

Through the pathway of “metabolic stabilization and immune support,” mulberry leaf extract provides essential background regulation within antiviral defense.

A. Upstream protection: preventing hyperglycemia-induced immune suppression

- Postprandial glycemic surges suppress neutrophil and macrophage phagocytic activity
- 1-DNJ in mulberry leaf inhibits α-glucosidase, delaying glucose release
- This reduces the acute hyperglycemia-driven suppression of innate immune responses

Significance: maintains effective activation of PRRs (pattern recognition receptors) and AMPs (antimicrobial peptides)

B. Midstream buffering: reducing glycation stress and inflammatory amplification

- Hyperglycemia accelerates formation of advanced glycation end products (AGEs)

- Binding of AGEs to their receptor (RAGE) activates NF-κB signaling, fueling inflammation and creating a favorable environment for viral replication
- Mulberry leaf extract limits AGE generation, thereby lowering NF-κB background activity

Significance: restricts inflammatory “boost factors” required for viral replication and spread

C. Downstream support: systemic anti-inflammatory and antioxidant effects

- Mulberry polyphenols exert antioxidant activity, scavenging ROS and alleviating oxidative stress
- Integrates with vitamin C, elderberry, and quercetin to strengthen the antioxidant network
- Reduces systemic inflammatory noise, preventing infection-driven systemic inflammatory storms

Significance: provides a stable background for immune polarity recalibration (vitamin D) and barrier repair (fish elastin peptides)

D. Synergistic significance

Within Module I, mulberry leaf extract functions as a “metabolic noise suppressor”:

- With quercetin and elderberry → enhances the efficiency of antiviral signaling

- With vitamin C and zinc → stabilizes immune cell function, reinforcing replication-blocking effects
- With elastin peptides → provides a low-glycation background, minimizing secondary ECM repair damage

Thus, while mulberry leaf is not a frontline viral blocker, it supports the immune-antiviral axis by maintaining metabolic homeostasis, immune functionality, and inflammatory buffering, thereby providing indispensable systemic support.

1.6) Antiviral Mechanisms of Zinc

Zinc is an essential trace element for maintaining immune competence and anti-infective capacity, exerting multi-dimensional roles in the prevention and management of respiratory infections.

Unlike simple nutritional supplementation, zinc operates through two primary antiviral pathways: direct inhibition of viral replication and indirect enhancement of host immunity.

A. Direct inhibition of viral replication

Replication of RNA viruses in host cells relies on key enzymes such as RNA-dependent RNA polymerase (RdRp). In vitro studies demonstrate that elevated intracellular zinc concentrations can directly inhibit RdRp activity, thereby reducing the replication efficiency of influenza, coronaviruses, and other RNA viruses.

Zinc also interferes with viral protein synthesis and assembly, lowering the number of

newly formed virions.

This mechanism functions as “cutting the production line,” preventing large-scale viral amplification within cells.

B. Stabilization of epithelial barrier function

The respiratory epithelium serves as the first physical defense against viral invasion. Zinc promotes the expression and repair of tight junction proteins such as occludin and claudin, preserving epithelial integrity. Barrier stability not only reduces opportunities for viral penetration but also decreases susceptibility to secondary bacterial infections.

C. Enhancement of innate and adaptive immunity

Zinc is indispensable for immune cell development and functional maintenance:

- Supports T lymphocyte differentiation, strengthening cellular immune responses
- Activates natural killer (NK) cells, enhancing early clearance of virus-infected cells
- Regulates monocyte and macrophage phagocytic activity, making innate responses more efficient

Through these mechanisms, zinc enables a broad-spectrum immune reinforcement that can contain viral spread at an early stage.

D. Synergy with quercetin

The antiviral potency of zinc is most pronounced when intracellular levels are sufficient. However, zinc ions have limited membrane permeability.

Quercetin, acting as a natural zinc ionophore, facilitates zinc transport into cells, thereby amplifying its RdRp inhibition. This “quercetin-zinc” combination represents a classic example of complementary nutritional synergy.

E. Clinical applicability

Zinc deficiency is well-documented to correlate with higher susceptibility to respiratory infections, prolonged disease course, and weakened immune responses.

Supplementation has been shown to shorten the duration of the common cold and acute upper respiratory tract infections, while reducing symptom severity.

Its antiviral benefits are particularly significant in children with immature immunity and elderly individuals with declining immune function.

Taken together, zinc integrates seamlessly into the core antiviral chain of four nutrients:

- Vitamin D: strengthens barrier and innate defenses via antimicrobial peptide induction
- Zinc: directly suppresses viral replication and enhances immune function
- Quercetin: provides multi-point interception and serves as a zinc ionophore
- Elderberry: blocks viral entry and shortens disease course

This synergy establishes a comprehensive defense network within the *Regulatory Axis I: Antiviral Immune Defense*.

1.7) Antiviral and Immune-Activating Mechanisms of Vitamin D

Vitamin D is widely recognized as a regulator of bone metabolism, yet it also plays a central role in antiviral defense within the respiratory system.

Acting through the vitamin D receptor (VDR), it integrates multiple functions - barrier maintenance, antimicrobial peptide induction, and immune polarity regulation - to form a pivotal shield against viral invasion in the airways.

A. Upregulation of antimicrobial peptides (AMPs)

One of vitamin D's most prominent antiviral mechanisms is its ability to induce AMP synthesis, particularly LL-37 (cathelicidin) and β-defensins.

- LL-37 binds directly to viral envelopes, disrupting their integrity and reducing infectivity
- β-defensins inhibit fusion between viral and host cell membranes, preventing viral genome release

This "frontline interception" equips epithelial cells with innate antiviral weaponry.

B. Enhancement of mucosal barrier function

Vitamin D regulates the expression of tight junction proteins, maintaining the physical integrity of the respiratory mucosa. Strengthened barrier function not only reduces viral penetration but also lowers susceptibility to secondary bacterial infections.
This structural resilience provides a firm foundation for subsequent antiviral responses.

C. Regulation of innate immune responses

Vitamin D promotes the maturation and functional optimization of macrophages and dendritic cells, enabling more efficient viral recognition and phagocytosis.
It also enhances the cytotoxic activity of natural killer (NK) cells, accelerating clearance of virus-infected cells.

D. Balancing adaptive immune polarity

At the adaptive level, vitamin D downregulates excessive Th1 and Th17 responses, thereby reducing pro-inflammatory cytokine release. In parallel, it increases the proportion of regulatory T cells (Tregs), enhancing tolerance and immune-regulation.
This rebalancing of immune polarity not only suppresses virus-driven inflammatory amplification but also fosters a microenvironment more conducive to tissue repair.

E. Clinical evidence and infection risk

Epidemiological studies consistently show that individuals with sufficient vitamin D status have a markedly lower incidence of respiratory tract infections compared with those

deficient. Multiple randomized controlled trials further confirm that vitamin D supplementation reduces the risk of acute respiratory infections, with especially strong benefits observed in children and the elderly. Collectively, these findings establish vitamin D as an “immune cornerstone” in respiratory health.

F. Synergistic significance

Vitamin D works in complementarity with zinc, quercetin, and elderberry:

- Provides the structural barrier foundation for upstream blockade by elderberry and quercetin
- Cooperates with zinc to enhance macrophage and T-cell antiviral functions
- Modulates immune polarity to prevent hyper-inflammatory responses, creating favorable conditions for downstream antioxidant and repair mechanisms

Through these mechanisms, vitamin D emerges not only as a direct antiviral enabler but also as a master regulator, bridging frontline defense with long-term immune balance and tissue protection.

1.8) Antioxidant and Barrier-Supporting Functions of Vitamin C

A. Buffering oxidative stress and maintaining redox homeostasis

During acute infection, large amounts of ROS/RNS generated by airway epithelial cells and phagocytes act as triggers that amplify inflammation and create a replication-

permissive environment for viruses.

Ascorbic acid (vitamin C) serves as a primary water-phase antioxidant, rapidly scavenging superoxide anions, hydroxyl radicals, and hypochlorous acid. In doing so, it reduces accumulation of lipid peroxidation products and aldehyde intermediates, lowering the activation threshold of multiple ROS-driven inflammatory pathways (e.g., NF-κB, p38/MAPK).

At the cellular level, vitamin C interacts with the glutathione / thioredoxin redox network in a “cross-cycle,” sustaining reducing capacity and NADPH-driven antioxidant efficiency. This minimizes oxidative imbalance-induced apoptosis of epithelial cells and protects barrier integrity.

B. The “antioxidant–antiviral” indirect inhibition chain

Viral replication relies on several host processes - such as endosomal acidification, nucleic acid replication microenvironments, and stress granule dynamics - that are highly sensitive to the cell’s redox state.

By lowering oxidative triggers and limiting the release of pro-inflammatory mediators and DAMPs, vitamin C raises the signal-to-noise ratio of innate immune clearance and weakens the replication-favorable environment.

Rather than targeting viral enzymes directly, this represents an “environmental restriction” strategy, indirectly suppressing viral life cycle progression.

C. Epithelial/endothelial barrier integrity and tight junction homeostasis

The mucosal and microvascular barriers of the respiratory tract serve as the first line of defense against pathogen penetration and exudative inflammation.

Vitamin C protects cytoskeletal and membrane proteins from oxidative damage, while promoting proper expression and assembly of tight junction proteins (occludin, claudin, ZO-1), thereby reducing permeability and edema.

At the basement membrane and ECM level, vitamin C functions as an essential cofactor for proline/lysine hydroxylases, stabilizing collagen triple helices and strengthening the mucosa-basement complex against mechanical stress.

This dual “biophysical + biochemical stabilization” enables epithelial barriers to withstand acute insults more effectively and provides a favorable environment for ventilation and repair.

D. Synergistic topologies with quercetin, zinc, and vitamin D

- With quercetin (lipid ↔ aqueous phases): quercetin primarily acts within lipid/membrane regions, while vitamin C operates in aqueous compartments. Vitamin C reduces oxidized quercetin radicals back to active forms, sustaining its activity in membranes and enabling a lipid-aqueous phase antioxidant synergy.
- With zinc: vitamin C decreases lipid peroxidation and protein carbonylation, preventing oxidative inactivation of tight junction proteins, which supports zinc’s role in barrier function and immune cell efficacy.

By lowering oxidative “noise,” vitamin C also enhances zinc’s replication-inhibition efficiency (e.g., RdRp suppression).

- With vitamin D: vitamin D promotes AMP production and epithelial repair via VDR signaling; vitamin C provides antioxidant and collagen metabolic support to consolidate barrier reconstruction.

  Together they create a dual stability model: functional stability (VDR-AMPs) + structural stability (TJ/ECM).

E. Clinical applicability in early infection

In the early and mid-phases of acute upper respiratory infections, vitamin C acts as a “co-factor” nutrient by:

- Reducing oxidative triggers that exacerbate symptoms and compromise epithelial barriers
- Enhancing the efficacy and tolerability of the quercetin–zinc antiviral scheme by lowering oxidative burden
- Offering critical buffering capacity in high oxidative-stress populations (elderly, smokers, individuals with metabolic syndrome), thereby shortening disease duration and improving recovery quality

F. Key takeaways

- Positioning: water-phase–dominant “systemic antioxidant + barrier guardian” foundation
- Core pathway: ROS/RNS clearance → lower redox activation threshold → stabilize TJ/ECM → strengthen quercetin–zinc antiviral efficiency
- Optimal synergy: quercetin (phase complementarity, regeneration cycle), zinc (barrier and replication dual support), vitamin D (dual stability of function and structure)
- Priority populations: those with high oxidative load or fragile barriers (elderly, smokers/second-hand smoke exposure, metabolic disorders, recurrent URTI history)

In essence, vitamin C does not exert antiviral effects through direct enzymatic inhibition, but through antioxidant defense, barrier stabilization, and synergistic amplification, thereby lowering replication-permissive conditions and inflammatory thresholds.
This allows vitamin C, together with quercetin, zinc, and vitamin D, to close the loop in the “antiviral and innate immune activation” module.

1.9) Summary of Module I : Antiviral and Innate Immune Activation

Antiviral defense and innate immune activation constitute the first and most critical step in respiratory health interventions. The primary objective is to block pathogen entry, suppress early replication, and strengthen mucosal defenses.

- **Vitamin D** enhances antimicrobial peptide production and fortifies mucosal barrier integrity, establishing a robust first-line defense.
- **Zinc** directly inhibits viral replication via RdRp suppression while supporting T and NK cell activity.
- **Quercetin**, through its multipoint interception mechanism, interferes with viral attachment, replication, and ion transport, while amplifying zinc’s antiviral efficacy.
- **Elderberry** binds viral glycoproteins to block adhesion, with clinical evidence demonstrating shortened illness duration and symptom relief.
- **Vitamin C** functions as an antioxidant and barrier-supporting factor, reducing ROS-driven triggers and regenerating polyphenols such as quercetin, creating a dual “antioxidant-antiviral” synergy.

Together, these five components construct a multi-layered antiviral defense line characterized by:

- **Barrier support**: vitamin D maintains mucosal stability and blocks viral entry routes
- **Replication inhibition**: zinc directly suppresses RdRp activity, weakening the replication chain
- **Synergy**: quercetin enhances zinc’s intracellular activity and broadly reduces viral viability
- **Symptom relief**: elderberry shortens disease course and alleviates clinical manifestations

- **Adjunctive support**: vitamin C provides redox buffering and barrier stabilization

This multi-component, multi-pathway integration model delivers a systemic solution for acute respiratory defense, while simultaneously laying the foundation for subsequent modules of inflammation control and structural repair.

- ✓ *Holick, M. F. (2007) Vitamin D deficiency. The New England Journal of Medicine, 357(3), 266-281.*

  - Systematically elaborates the central role of vitamin D in immune function, supporting its mechanism of upregulating antimicrobial peptides via VDR and enhancing antiviral defense in the respiratory tract
- ✓ *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.*

  - Large-scale meta-analysis demonstrates that vitamin D supplementation significantly reduces the risk of acute respiratory tract infections, especially effective in vitamin D-deficient populations
- ✓ *te Velthuis, A. J., van den Worm, S. H., Sims, A. C., et al. (2010) Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathogens, 6(11), e1001176.*

  - Demonstrates that zinc directly inhibits viral RNA polymerase activity, while ionophores such as quercetin enhance the intracellular antiviral efficacy of zinc
- ✓ *Maares, M., & Haase, H. (2016) Zinc and immunity: An essential interrelation. Archives of Biochemistry and Biophysics, 611, 58-65.*

- Reviews the multidimensional role of zinc in the immune system, including T cells, NK cells, and epithelial barrier stability

✓ *Colunga Biancatelli, R. M. L., Berrill, M., & Marik, P. E. (2020) The antiviral properties of vitamin C. Expert Review of Anti-infective Therapy, 18(2), 99-101.*

- Primarily focused on vitamin C, but also highlights the synergistic antiviral effects of quercetin and zinc

✓ *Zakay-Rones, Z., Varsano, N., Zlotnik, M., et al. (1995) Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (Sambucus nigra L.) during an outbreak of influenza B Panama. The Journal of Alternative and Complementary Medicine, 1(4), 361-369.*

- First clinical study demonstrating that elderberry extract shortens influenza illness duration and alleviates acute respiratory infection symptoms

✓ *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.*

- Randomized controlled trial confirming that elderberry reduces the duration and symptom burden of upper respiratory infections in travelers

✓ *Colunga Biancatelli, R. M. L., Berrill, M., Catravas, J. D., & Marik, P. E. (2020) Quercetin and vitamin C: An experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Frontiers in Immunology, 11, 1451.*

- Explains quercetin’s multi-target antiviral mechanisms and its role as a zinc ionophore, while proposing the therapeutic value of its combination with vitamin C

2) Module II - Inflammation, Inflammasome, and Allergic Response Regulation

In respiratory diseases, inflammation is both protective and pathogenic. While it assists in pathogen clearance, loss of control precipitates local tissue injury and functional decline.

In the acute phase, excessive responses may trigger a cytokine storm, causing alveolar exudation and respiratory distress; in the chronic phase, persistent low-grade inflammation drives airway remodeling, fibrosis, and airflow limitation, sustaining disease persistence and recurrence.

The NLRP3 inflammasome serves as a molecular hub for inflammatory amplification: by activating caspase-1, it promotes the abundant release of IL-1β and IL-18, aggravating tissue damage. In parallel, respiratory allergic diseases (e.g., allergic rhinitis, asthma) feature excessive mast-cell degranulation with release of histamine, leukotrienes, and prostaglandins, further escalating inflammation and provoking airway hyper-reactivity.

Within this module, components of *Keyora LungOra 8 in 1* exert targeted nutraceutical pharmacology:

- **Quercetin**: suppresses NF-κB and NLRP3 activation; stabilizes mast cells to reduce release of allergic mediators

- **Bromelain**: modulates cytokine networks, inhibits pro-inflammatory signaling, and shapes immune-cell activity
- **Fish cardiac bulb–derived elastin peptides**: repair extracellular matrix and basement membrane integrity, limit leakage and diffusion of inflammatory mediators, lower the risk of cytokine storm, and provide a stable tissue background for immune regulation
- **Elderberry**: polyphenols down-regulate NF-κB signaling and mitigate airway inflammation
- **Mulberry leaf**: reduces the generation of advanced glycation end-products (AGEs) and down-regulates basal NF-κB activity, thereby buffering “metabolism-driven inflammatory noise” and reinforcing the systemic anti-inflammatory/antioxidant network
- **Vitamin C**: scavenges ROS to indirectly prevent inflammasome activation and synergizes with quercetin to enhance anti-inflammatory efficacy
- **Vitamin D**: via VDR, rebalances T-cell polarity - attenuating excessive Th17 responses while enhancing Treg function - to lower the risk of immune disequilibrium
- **Zinc**: supports immune homeostasis and facilitates post-inflammatory tissue recovery

Regulating inflammation, inflammasome activity, and allergic responses is essential not only for controlling acute symptoms and limiting tissue injury, but also for achieving long-term disease stability.

The objective of *Keyora LungOra 8 in 1* in this module is to establish an integrated shield

of anti-inflammation, anti-allergy, and immune balance through multi-component, multi-target synergy.

2.1) Quercetin and Its Dual Role in Inflammasome Regulation and Allergic Response Control

Quercetin, a representative flavonoid, has been extensively studied in respiratory nutritional pharmacology. Its biological relevance extends far beyond antioxidant and antiviral effects; it also plays a central role in inflammatory signaling modulation and allergic response attenuation.

Pathological evidence indicates that the amplification of respiratory inflammation is tightly linked to two processes: hyperactivation of the NLRP3 inflammasome and mast cell–mediated allergic reactions.

These mechanisms respectively drive acute cytokine storms and chronic allergic inflammation. Quercetin has demonstrated the ability to intervene in both domains simultaneously:

- Inhibiting the NF-κB/NLRP3 signaling axis, thereby reducing IL-1β and IL-18 release.
- Stabilizing mast cell membranes, lowering histamine and leukotriene release, and alleviating clinical symptoms of allergic rhinitis and asthma.

Through this dual pathway of inflammasome control and allergic mediator regulation, quercetin provides broad-spectrum support across both acute and chronic phases of respiratory disease.

A. Suppression of NF-κB Signaling

NF-κB functions as a central transcription factor in respiratory inflammation, orchestrating the synthesis of multiple mediators such as IL-6, TNF-α, and COX-2. Viral infection, ROS accumulation, or cellular stress can trigger IκB degradation, leading to NF-κB activation. Quercetin interferes with IκB phosphorylation and nuclear translocation, markedly reducing pro-inflammatory cytokine levels and preventing excessive inflammatory cascades. This mechanism has been validated in asthma and COPD models, where quercetin lowered mucosal immune cell infiltration, cytokine release, and airway hyper-responsiveness.

B. Inhibition of NLRP3 Inflammasome Activation

The NLRP3 inflammasome is a molecular hub for inflammation amplification, requiring ROS accumulation, ionic imbalance, and mitochondrial dysfunction for its activation. Quercetin attenuates these triggers by scavenging ROS, modulating mitochondrial homeostasis, and suppressing upstream signals, thereby limiting caspase-1 activation and downstream IL-1β/IL-18 release.

In preclinical models of ARDS and viral pneumonia, quercetin significantly reduced IL-1β levels in alveolar fluid, lowering alveolar leakage and the risk of cytokine storm.

C. Mast Cell Stabilization and Inhibition of Allergic Mediators

Quercetin also exerts well-characterized anti-allergic effects by:

- Preventing mast cell degranulation
- Inhibiting the release of histamine, leukotrienes, and prostaglandin D_2
- Down-regulating FcεRI-mediated allergic signaling pathways

These actions directly alleviate symptoms such as nasal congestion, sneezing, and bronchospasm, thereby improving clinical outcomes and quality of life for patients with allergic rhinitis and asthma.

D. Synergy within the Module II Framework

- With Vitamin C: Vitamin C regenerates oxidized quercetin, prolonging its anti-inflammatory activity and creating an “antioxidant–anti-inflammatory” coupling.
- With Vitamin D: Both attenuate the Th17/IL-17 inflammatory axis while enhancing Treg functionality, thereby restoring immune polarity.
- With Elderberry: Both target NF-κB signaling, with quercetin acting on upstream checkpoints and elderberry polyphenols reinforcing downstream suppression, yielding cumulative inhibitory effects.

E. Clinical Applicability

Quercetin demonstrates therapeutic value across a spectrum of respiratory diseases characterized by inflammation and allergy:

- Acute phase: reduces inflammatory mediator release and lowers symptom intensity.
- Chronic phase: mitigates persistent airway inflammation and delays structural remodeling.
- Allergic comorbidities: stabilizes mast cells to improve allergic rhinitis and asthma symptoms.

2.2) Bromelain in Anti-Inflammatory and Immunoregulatory Mechanisms

Bromelain, a proteolytically active enzyme complex derived from the stem of pineapple (2400 GDU/g), is conventionally recognized for its mucolytic and ventilatory benefits. Yet, accumulating evidence highlights its broader role in inflammation regulation and allergic response intervention.

By modulating cytokine networks, attenuating pro-inflammatory signaling, and shaping immune-cell activity, bromelain participates in the suppression of NF-κB–driven inflammatory cascades as well as the indirect activation pathways of the NLRP3 inflammasome.

In addition, bromelain exhibits anti-allergic properties by inhibiting mast-cell degranulation

and reducing histamine release, thereby alleviating airway hyper-responsiveness and rhinitis symptoms.

Thus, bromelain is not merely a tool for mucolytic support but a multi-dimensional nutrient with anti-inflammatory, immunomodulatory, and anti-allergic attributes.
Within the Keyora LungOra 8 in 1 framework, it acts synergistically with quercetin, vitamin D, and vitamin C to form an integrated network that spans inflammation, inflammasome regulation, and allergic control - providing support across both acute and chronic phases of respiratory disease.

A. Suppression of Pro-Inflammatory Mediator Release

In acute respiratory infections, excessive release of pro-inflammatory mediators drives tissue injury.

- Bromelain significantly lowers levels of PGE_2, COX-2, IL-1β, IL-6, and TNF-α
- Reduces immune-cell infiltration and tissue destruction
- Interrupts early amplification loops of the inflammatory cascade

Significance: Acts as a *circuit breaker* for inflammation, reducing the extent of acute damage.

B. Cytokine Balance and Resolution Support

- Promotes secretion of IL-10 and other anti-inflammatory mediators

- Reinforces negative feedback mechanisms to suppress chronic low-grade inflammation
- Helps restore post-inflammatory tissue homeostasis

Significance: Establishes an intrinsic *braking system* to prevent persistence of inflammation.

C. Indirect Suppression of NLRP3 Inflammasome Activation

- ROS and pro-inflammatory mediators are primary activators of the NLRP3 inflammasome
- Bromelain reduces ROS generation and dampens inflammatory triggers, thereby indirectly limiting NLRP3 activation
- Attenuates excessive IL-1β and IL-18 release, reducing risks of alveolar leakage and respiratory distress

Significance: Blocks initiation of a cytokine storm at its signaling roots.

D. Immunocellular Modulation

- Shifts macrophage polarization by reducing pro-inflammatory M1 subsets while enhancing reparative M2 phenotypes
- Supports lymphocyte proliferation and natural killer (NK) cell function
- Reorients immune responses from destructive toward reparative modes

Significance: Redirects the inflammatory milieu toward resolution rather than exacerbation.

E. Synergy within the Module II Framework

- With Quercetin → Joint inhibition of NF-κB signaling and inflammasome activation
- With Vitamin C → Coordinated reduction of ROS burden
- With Vitamin D → Enhanced efficiency of immune-polarity rebalancing
- With Elderberry → Polyphenol-based and protease-based anti-inflammatory actions reinforce each other

Overall Role: In the context of Module II, bromelain functions as both an *inflammatory milieu shaper* and an *immune equilibrium stabilizer*.

F. Summary

The value of bromelain in inflammation regulation lies not in *single-node inhibition* but in its capacity to build a relatively homeostatic immune environment through multi-tiered intervention. It acts acutely by breaking amplification loops to limit tissue damage and chronically by balancing cytokines and modulating macrophage lineages to prevent persistence of inflammation.

By indirectly suppressing NLRP3 activation, bromelain also lowers the risk of cytokine storm, thus providing critical protection across acute and chronic phases of respiratory

disease. Acting in synergy with quercetin, vitamin C, vitamin D, and elderberry, bromelain serves as an *environmental architect and immunological stabilizer within Module II*, enabling Keyora LungOra 8 in 1 to achieve its multi-dimensional goals of anti-inflammation, anti-allergy, and immune homeostasis.

2.3) Fish Cardiac Bulb-Derived Elastin Peptides in “Structure-Inflammation Crosstalk” Regulation

In respiratory inflammation, structural damage and inflammatory amplification frequently form a vicious cycle: acute inflammation disrupts the extracellular matrix (ECM) and basement membrane, and the resulting degradation fragments act as danger-associated molecular patterns (DAMPs) that stimulate immune cells and activate inflammasomes, particularly NLRP3. This not only exacerbates acute injury but also drives chronic low-grade inflammation and fibrotic progression.

Fish cardiac bulb-derived elastin peptides, enriched in desmosine and isodesmosine, provide the essential substrates for elastin resynthesis and crosslinking stability. Their significance lies not in merely supplementing proteins but in accelerating matrix repair, reducing the release of degradation fragments, and stabilizing barrier structures, thereby disrupting the feedback loop of “injury-inflammation-reinforced injury.”

Within the Module II framework, these peptides function as disruptors of structure-inflammation crosstalk, complementing quercetin, bromelain, and vitamin D: while the

latter directly suppress inflammatory signaling, elastin peptides intervene at the structural origin, lowering the activation threshold for inflammasomes and allergic responses.

A. Vicious cycle of ECM degradation and inflammatory amplification

In acute airway inflammation, proteases and ROS induce elastin fiber rupture and basement membrane breakdown. The resulting degradation fragments serve as DAMPs, recognized by immune cells and driving NLRP3 inflammasome activation, which in turn triggers excessive IL-1β and IL-18 release.

Conclusion: structural breakdown is not only a consequence but also a driver of inflammation.

B. Elastin peptide supplementation: reducing upstream triggers

Fish elastin peptides, rich in desmosine and isodesmosine, provide characteristic substrates for elastin fiber regeneration.

- Facilitate rapid ECM repair through replenishment of these residues
- Prevent continuous release of degradation fragments
- Reduce inflammasome activation signals at their source

Significance: interrupts the vicious cycle at the upstream level of the inflammatory pathway.

C. Barrier stabilization and reduction of allergic inflammation

Basement membrane disruption facilitates allergen and pathogen penetration, heightening mast-cell and eosinophil activation.

- Elastin peptides support restoration of basement membrane and elastin fiber integrity
- Reduce opportunities for allergen infiltration, alleviating allergic responses
- Complement quercetin’s mast-cell stabilizing effects

Significance: decreases allergic sensitivity and mitigates airway hyper-responsiveness.

D. Synergistic roles within the Module II framework

- With vitamin C → “substrate + cofactor” pairing to improve ECM repair quality and reduce fibrosis
- With bromelain → structural repair plus reduction of inflammatory mediators, establishing bidirectional control of damage and repair
- With vitamin D and zinc → cooperative support for immune polarity and barrier stability, further reducing risks of chronic inflammation

Summary: *In Module II framework*, fish cardiac bulb-derived elastin peptides are positioned as structural disruptors of inflammation crosstalk. By repairing ECM, reducing degradation fragments, and stabilizing the basement membrane, they indirectly suppress overactivation of inflammasomes and allergic pathways.

Their unique value lies in not acting as direct anti-inflammatory agents, but in regulating inflammation through structural reconstruction - providing deep, long-term support for respiratory homeostasis.

2.4) Elderberry and Polyphenol-Driven Modulation of Inflammation and Allergic Responses

A. Inhibition of the NF-κB Pathway

Elderberry is rich in anthocyanins and polyphenols, bioactive compounds that inhibit IκB phosphorylation and reduce the nuclear translocation of NF-κB. This results in decreased expression of key pro-inflammatory mediators such as TNF-α, IL-6, and IL-8.
By dampening this pathway, elderberry attenuates early amplification of inflammation during acute infection and helps buffer the chronic inflammatory drive in long-standing airway diseases.

B. Indirect Modulation of Inflammasome Activity

Through its antioxidant properties, elderberry polyphenols lower intracellular ROS levels, thereby reducing upstream signals that activate the NLRP3 inflammasome.
By concurrently suppressing pro-inflammatory cytokines, elderberry indirectly limits caspase-1 activation and the maturation and release of IL-1β.
When combined with quercetin and vitamin C, elderberry contributes an additional tier to the “negative regulatory network” of inflammasome control.

C. Anti-Allergic Potential

Evidence suggests elderberry may alleviate allergic inflammatory manifestations:

- Anthocyanins suppress mast-cell degranulation and reduce histamine release
- Lower IL-4 and IL-13 expression, attenuating eosinophilic inflammation and excessive IgE synthesis

Although its anti-allergic strength is somewhat milder compared to quercetin or bromelain, elderberry functions as a complementary and reinforcing component within the formula.

D. Synergies within Module II

- With quercetin: both suppress NF-κB, but with distinct phytochemical profiles - anthocyanins (elderberry) and flavonols (quercetin) - yielding additive inhibition of inflammatory signaling
- With vitamin C: anthocyanins act predominantly in lipid-membrane domains, while vitamin C operates in aqueous phases and regenerates oxidized anthocyanins, creating a cross-phase antioxidant synergy
- With bromelain: elderberry attenuates NF-κB–driven cytokine release, while bromelain promotes IL-10 expression; together they establish a dual pathway of “pro-inflammatory downregulation and anti-inflammatory upregulation”

E. Clinical Relevance

Randomized trials have demonstrated that elderberry supplementation shortens the duration of influenza and upper respiratory tract infections, while alleviating symptoms such as fever, sore throat, and nasal congestion. These clinical benefits reflect not only its antiviral capacity but also its ability to lower inflammatory mediator levels. Elderberry is thus positioned as an adjunct during acute inflammatory phases and as supportive care for patients with coexisting mild-to-moderate allergic inflammation.

F. Summary

The regulatory actions of elderberry in inflammation and allergic responses include:

- Inhibition of NF-κB signaling and reduction of pro-inflammatory cytokines
- Indirect suppression of NLRP3 inflammasome activation
- Supportive attenuation of mast-cell activity and eosinophilic inflammation
- Integration into a synergistic anti-inflammatory network with quercetin, vitamin C, and bromelain

Elderberry is characterized by moderate anti-inflammatory potency but complementary antioxidant and anti-allergic pathways. Within Keyora LungOra 8 in 1, it functions as a buffering agent against acute inflammation while serving as a stabilizing element of the broader anti-inflammatory network.

2.5) Mulberry Leaf and the Regulation of Metabolism–Inflammation Coupling

In respiratory diseases, inflammation is not only driven by pathogens but is also strongly influenced by the metabolic environment. Hyperglycemia and the accumulation of advanced glycation end-products (AGEs) amplify inflammation through the RAGE–NF-κB axis and indirectly activate the NLRP3 inflammasome.

This means that even under equivalent pathogenic stimulation, a dysregulated metabolic background leads to stronger inflammatory responses, worsening lung injury and allergic reactivity.

Mulberry leaf extract, rich in 1-deoxynojirimycin (1-DNJ) and polyphenols, inhibits α-glucosidase, significantly blunts postprandial glucose spikes, and reduces AGE formation. By mitigating “metabolic-inflammatory coupling,” it lowers the activation threshold of the NLRP3 inflammasome while weakening the pro-inflammatory background that fuels allergic responses.

Within *Module II framework*, mulberry leaf functions as a “metabolic-inflammatory buffer”: rather than directly suppressing inflammatory mediators, it stabilizes metabolic status to prevent amplification of inflammation and inflammasome activity, complementing the direct immunomodulatory actions of quercetin, bromelain, vitamin D, and other agents.

A. Buffering the Disruptive Effect of Postprandial Hyperglycemia

Acute hyperglycemia during infection suppresses neutrophil and macrophage phagocytic activity and triggers the release of additional pro-inflammatory cytokines.

- 1-DNJ in mulberry leaf inhibits α-glucosidase, delaying carbohydrate breakdown and absorption
- Reduces postprandial glucose peaks and insulin surges
- Breaks the cycle of “hyperglycemia → immune suppression → inflammation exacerbation”

Significance: keeps inflammation at a manageable level and prevents hyperglycemia-driven escalation.

B. Inhibition of the AGE–RAGE Inflammatory Axis

Chronic or recurrent hyperglycemia accelerates AGE formation. AGE–RAGE binding persistently activates NF-κB signaling and amplifies NLRP3 inflammasome activation.

- Mulberry polyphenols inhibit AGE generation and reduce AGE–RAGE binding
- This decreases NF-κB–dependent cytokine production
- Indirectly lowers IL-1β and IL-18 release from inflammasome activation

Significance: diminishes the “background fuel” that sustains inflammasome-driven tissue injury.

C. Antioxidant and Anti-Allergic Support

- Mulberry flavonoids and polyphenols exert antioxidant effects, reducing ROS accumulation
- Because ROS are major triggers of NLRP3 activation, this indirectly dampens inflammasome signaling
- Antioxidant activity also mitigates mast-cell degranulation, reducing histamine and leukotriene release

Significance: provides dual buffering at the intersection of inflammation and allergic reactivity.

D. Synergistic Interactions within Module II

- With quercetin: quercetin directly suppresses NF-κB and NLRP3, while mulberry leaf weakens these pathways indirectly through metabolic control
- With bromelain: mulberry stabilizes the metabolic–inflammatory background, while bromelain reduces inflammatory mediators directly, creating front–back synergy
- With vitamin C: complementary in ROS scavenging and inflammasome inhibition
- With vitamin D and zinc: ensures immune polarity and tissue repair occur within a low-inflammatory environment

Summary: Mulberry leaf extract is positioned in *Module II* as a "metabolic background inflammation buffer." By lowering glycemic fluctuations, inhibiting the AGE-RAGE axis,

reducing ROS-driven inflammasome activation, and attenuating allergic responses, it decreases the threshold for inflammatory overactivation at the systemic level.

In synergy with direct anti-inflammatory agents, mulberry ensures that Keyora LungOra 8 in 1 not only “quenches the fire” but also “controls the fuel,” preventing recurrent cycles of uncontrolled inflammation.

2.6) Vitamin C as an Antioxidant Core and Indirect Modulator of Inflammation and Allergic Responses

A. Buffering Oxidative Stress to Lower the Inflammatory Activation Threshold

Oxidative stress serves as an upstream driver of both inflammation and inflammasome activation. Excessive ROS induce NF-κB activation and trigger NLRP3 inflammasome assembly. As the principal water-soluble antioxidant, vitamin C:

- Rapidly scavenges superoxide anions, hydroxyl radicals, and hydrogen peroxide
- Reduces the accumulation of lipid peroxidation products such as MDA and 4-HNE
- Sustains the efficiency of intracellular glutathione and thioredoxin cycles

By lowering ROS levels, vitamin C indirectly suppresses amplification of inflammatory signaling and activation of the inflammasome, thereby reducing excess IL-1β and IL-18 release.

B. Indirect Down-Regulation of NF-κB and Pro-Inflammatory Mediators

Although vitamin C does not act directly on NF-κB, its antioxidant action attenuates upstream triggers (ROS, MAPK signaling), thereby indirectly reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8. While its direct efficacy is less pronounced than that of quercetin or elderberry, vitamin C plays a crucial role in maintaining a low inflammatory threshold.

C. Supportive Regulation of Allergic Responses

Vitamin C lowers mast-cell sensitivity:

- Clinical studies show that vitamin C deficiency increases mast-cell degranulation, while supplementation reduces histamine release
- Through antioxidant activity, it attenuates the ROS-mediated amplification of IgE-dependent reactions, thereby decreasing airway hyper-reactivity

This confers protective effects in allergic rhinitis and asthma populations.

D. Synergy with Other Nutrients

- With quercetin: vitamin C regenerates the active form of quercetin, prolonging its anti-inflammatory and anti-allergic efficacy
- With bromelain: the two act from complementary angles - ROS buffering versus cytokine balance - to jointly suppress inflammasome activation

- With elderberry: complements polyphenols in antioxidant pathways, enhancing NF-κB inhibition
- With vitamin D: by sustaining a low-inflammation, low-oxidative environment, vitamin C enables vitamin D to more effectively rebalance immune polarity and promote Treg function

E. Clinical Applicability

Supplementation with vitamin C has been associated with reductions in inflammatory markers, particularly CRP and IL-6, in infection recovery phases or chronic inflammatory states. In allergic populations, its value lies in reducing symptom severity and enhancing the efficacy of anti-allergic medications.

F. Summary

Vitamin C regulates inflammation, inflammasome activation, and allergic responses primarily through three pathways:

- Buffering ROS to indirectly inhibit NLRP3 inflammasome activity
- Attenuating upstream NF-κB activation to reduce pro-inflammatory mediator release
- Stabilizing mast-cell thresholds to limit histamine release

In the formulation, vitamin C is not positioned as a stand-alone anti-inflammatory agent but as an “antioxidant core and synergistic amplifier,” reinforcing the broader anti-

inflammatory and anti-allergic network created by quercetin, vitamin D, bromelain, and elderberry.

2.7) Vitamin D in Immunological Polarity and Inflammation Regulation

In the regulation of respiratory inflammation, both the balance of immune responses and the degree of inflammasome activation determine whether disease progression moves toward resolution or exacerbation. Vitamin D, acting via its nuclear receptor VDR (Vitamin D Receptor), exerts multi-layered control across the immune system.

On one hand, it promotes Treg cell differentiation and restrains excessive Th17 responses, preventing immune polarization from tipping toward uncontrolled inflammation.

On the other hand, it down-regulates NF-κB and JAK/STAT signaling, thereby indirectly attenuating overactivation of the NLRP3 inflammasome and limiting abnormal release of IL-1β and IL-18. In parallel, Vitamin D strengthens epithelial integrity by enhancing tight junction protein expression, reducing allergen penetration and dampening allergic activation.

Within *Module II*, Vitamin D is positioned as a regulator of immune polarity and inflammatory thresholds. Its role is not simply to suppress inflammation but to recalibrate the activation threshold of immune and inflammasome pathways - ensuring that inflammation remains effective for pathogen clearance while avoiding excessive

amplification.

This makes Vitamin D a central hub component of Keyora LungOra 8 in 1 in the control of inflammation and allergic responses.

A. VDR-mediated immune polarity recalibration

Immune disequilibrium in respiratory disease often manifests as overactive Th17/Th1 responses alongside insufficient Treg function.

- Through VDR engagement, Vitamin D up-regulates Treg cells and strengthens immune tolerance
- Simultaneously, it suppresses Th17 activity and reduces secretion of IL-17 and other inflammatory mediators
- This shifts the immune response from a destructive profile toward balance and repair

Significance: By lowering chronic inflammatory tone, Vitamin D helps mitigate airway remodeling and fibrotic progression.

B. Inflammasome and cytokine storm suppression

- Vitamin D inhibits NF-κB and JAK/STAT signaling, leading to reduced IL-6 and TNF-α levels
- These cytokines are critical upstream activators of the NLRP3 inflammasome

- By attenuating these signals, Vitamin D indirectly suppresses IL-1β and IL-18 overproduction, reducing the risk of cytokine storm

Significance: Provides protective benefit in acute settings such as ARDS risk during severe infections.

C. Barrier fortification and allergic response buffering

- Vitamin D promotes expression of tight junction proteins (occludin, claudin, ZO-1)
- This stabilizes the epithelium and basement membrane, reducing trans-barrier allergen entry
- In turn, it lessens mast-cell and eosinophil hyperactivation, thereby alleviating allergic manifestations

Significance: Reduces airway hyper-responsiveness, improving the context of asthma and allergic rhinitis.

D. Synergistic roles with other nutrients

- With quercetin and elderberry: jointly inhibit NF-κB signaling to reduce pro-inflammatory cytokine release
- With bromelain: Vitamin D rebalances immune polarity while bromelain reduces inflammatory mediators, producing a two-pronged buffering effect

- With fish cardiac bulb-derived elastin peptides: Vitamin D stabilizes immune polarity while elastin peptides restore structural integrity, together disrupting the cycle of “inflammation-damage-re-inflammation”

E. Summary

Vitamin D in *Module II functions* as a core regulator of immune polarity and inflammasome buffering. Through the integrated pathway of “VDR signaling → immune polarity balance → indirect inflammasome suppression → barrier stabilization,” it acts at the top tier of immune regulation.

Its distinctive value lies in moving beyond simple anti-inflammation to recalibration of system thresholds, ensuring that immune responses effectively clear pathogens without inflicting excessive tissue damage.

2.8) Zinc as a Key Micronutrient in Inflammation Homeostasis and Inflammasome Suppression

A. Maintaining immune-inflammation balance

Zinc acts as a cofactor for numerous immune-related enzymes and transcription factors, making it indispensable for balancing immune activity and inflammation control.

Zinc deficiency is frequently characterized by the paradoxical coexistence of excessive pro-inflammatory mediator release and weakened immune competence.

Evidence shows that zinc can:

- Down-regulate TNF-α and IL-6 to reduce inflammatory burden
- Support balanced expression of IL-2 and IFN-γ to preserve immune effectiveness
- Regulate macrophage and monocyte function, thereby preventing uncontrolled amplification of inflammatory cascades

B. Suppression of NLRP3 inflammasome activation

Zinc inhibits excessive activation of the NLRP3 inflammasome through several mechanisms:

- Reducing ROS load via metallothionein induction, which scavenges free radicals and diminishes upstream inflammasome triggers
- Regulating ion-channel homeostasis, particularly potassium efflux and calcium signaling, thereby attenuating the molecular conditions necessary for inflammasome assembly
- Lowering IL-1β and IL-18 secretion, which prevents acute-phase inflammatory escalation

In respiratory disease models, zinc supplementation significantly reduces IL-1β concentrations in bronchoalveolar lavage fluid and alleviates inflammatory tissue injury.

C. Role in allergic responses

Zinc directly modulates mast-cell and eosinophil function:

- Deficiency increases mast-cell degranulation and histamine release
- Adequate zinc stabilizes cell membranes, reducing secretion of histamine and leukotrienes
- Zinc also down-regulates Th2-driven inflammatory bias, thereby dampening allergic reactivity

These mechanisms support zinc’s adjunctive role in allergic conditions such as rhinitis and asthma.

D. Synergistic interactions with other nutrients

- With quercetin: quercetin acts as a zinc ionophore, enhancing cellular uptake and amplifying zinc’s inhibition of both inflammasome activation and viral RdRp
- With vitamin C: vitamin C reduces oxidative stress, allowing zinc to act more efficiently in inflammasome suppression
- With vitamin D: both nutrients cooperate to maintain immune competence and immune polarity, particularly in chronic inflammatory states
- With bromelain: zinc sustains cytokine homeostasis while bromelain strengthens anti-inflammatory negative feedback, forming a complementary loop

E. Clinical applicability

- Acute inflammation: zinc supplementation reduces inflammatory intensity post-infection and shortens symptom duration

- Chronic inflammation: in COPD and asthma, serum zinc levels inversely correlate with systemic inflammatory markers
- Allergic populations: zinc supplementation lowers the frequency and severity of allergic rhinitis and asthma symptoms

F. Summary

Zinc's role in Module II is defined by its contribution to inflammatory homeostasis, inflammasome suppression, and allergic modulation:

- Maintaining the equilibrium between immune activation and inflammation
- Preventing NLRP3 overactivation by lowering ROS and stabilizing ion flux
- Stabilizing mast-cell and eosinophil activity to reduce allergic hyper-responsiveness

Within the Keyora LungOra 8 in 1 system, zinc serves as a core micronutrient for inflammation homeostasis, working in synergy with quercetin, vitamin C, vitamin D, elderberry, and bromelain to establish a multi-layered defense network encompassing anti-inflammation, anti-allergy, and immune equilibrium.

2.9) Module II Summary: Regulation of Inflammation, Inflammasome Activation, and Allergic Responses

Both acute exacerbations and chronic progression of respiratory diseases are fundamentally linked to dysregulated inflammation and excessive inflammasome

activation.

Excessive inflammatory responses can trigger a cytokine storm, leading to alveolar leakage and acute injury, whereas chronic low-grade inflammation and allergic responses drive airway remodeling and functional decline.

Within this module, *Keyora LungOra 8 in 1* integrates the synergistic actions of quercetin, bromelain, fish cardiac bulb-derived elastin peptides, elderberry, mulberry leaf, vitamin D, vitamin C, and zinc to establish a comprehensive defense system centered on anti-inflammation, anti-allergy, and immune balance.

- **Quercetin**: Dual-action compound that suppresses NF-κB and NLRP3 inflammasome activation, reducing IL-1β and IL-18 release, while stabilizing mast cells to lower histamine and leukotriene output, directly alleviating allergic reactions.
- **Bromelain**: Reduces COX-2, TNF-α, and IL-6, while promoting IL-10 upregulation; additionally suppresses mast-cell degranulation and eosinophilic inflammation, mitigating rhinitis and asthma symptoms.
- **Fish cardiac bulb-derived elastin peptides**: Provide characteristic residues (desmosine, isodesmosine) for ECM repair, reducing release of degradation fragments that activate inflammasomes; also restore basement-membrane integrity to limit allergen penetration and indirectly attenuate allergic inflammation.
- **Elderberry**: Anthocyanins and polyphenols down-regulate NF-κB signaling, indirectly reduce inflammasome activity, and exhibit moderate anti-allergic potential.

- **Mulberry leaf**: By inhibiting α-glucosidase, lowers postprandial glucose spikes and AGE formation, thereby reducing AGE–RAGE-driven NF-κB and NLRP3 activation; its polyphenols further add antioxidant and anti-allergic benefits.
- **Vitamin D**: Modulates immune polarity through VDR signaling, suppresses Th1/Th17 hyperactivation, enhances Treg function, and indirectly inhibits NLRP3 activation via NF-κB and JAK/STAT down-regulation.
- **Vitamin C**: As a water-phase antioxidant core, eliminates ROS, indirectly suppresses inflammasome assembly, reduces mast-cell sensitivity, and regenerates quercetin to extend its anti-inflammatory activity.
- **Zinc**: Lowers ROS via metallothionein induction, stabilizes ion channels, and suppresses inflammasome activation; also stabilizes mast-cell membranes, reduces allergic mediator release, and sustains immune homeostasis.

Together, these ingredients form complementary layers of defense:

- **Inflammatory suppression layer**: Quercetin, vitamin D, elderberry, elastin peptides - NF-κB inhibition, ECM repair, inflammasome control
- **Antioxidant buffering layer**: Vitamin C, zinc, mulberry leaf - ROS scavenging, AGE–RAGE suppression
- **Anti-allergic layer**: Quercetin, bromelain, vitamin C, elastin peptides - mast-cell stabilization, allergen barrier protection

- **Immune-balancing layer**: Vitamin D, zinc, mulberry leaf - polarity recalibration, background noise reduction

Clinical significance

- Acute phase: Mitigates cytokine storm risk, alleviates alveolar injury, reduces symptom severity
- Chronic phase: Buffers low-grade inflammation and fibrosis, stabilizes airway function
- Allergic populations: Reduces allergic mediator release, lowers airway hyper-reactivity, improves long-term disease control

Conclusion

The *Module II* Regulation of Inflammation, Inflammasome Activation, and Allergic Responses strategy positions *Keyora LungOra 8 in 1* as a tri-dimensional regulator of inflammation, allergy, and immune homeostasis.

It provides a multi-layered defense system capable of preventing acute inflammatory escalation while attenuating chronic disease progression, thereby offering evidence-based support for both acute management and long-term maintenance of respiratory health.

✓ *Kim, H. P., Mani, I., Iversen, L., & Ziboh, V. A. (1998) Effects of naturally-occurring flavonoids and biflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea-pigs. Prostaglandins,*

Leukotrienes and Essential Fatty Acids, 58(1), 17-24.

- Demonstrates the inhibitory effects of quercetin and other flavonoids on COX and LOX pathways, providing experimental evidence for their anti-inflammatory mechanisms

✓ *Li, C., & Schluesener, H. (2017) Health-promoting effects of the flavonoid quercetin in animal and human studies. Current Medicinal Chemistry, 24(31), 3559-3579.*

- Reviews the anti-inflammatory and anti-allergic effects of quercetin, including suppression of NF-κB and inflammasome activation as well as stabilization of mast cells

✓ *Yin, K., & Agrawal, D. K. (2014) Vitamin D and inflammatory diseases. Journal of Inflammation Research, 7, 69-87.*

- Explains how vitamin D, through VDR signaling, regulates inflammatory pathways and immune polarity

✓ *Panagiotou, G., Tee, S. A., Ihsan, Y., et al. (2020) Low serum 25-hydroxyvitamin D levels in patients hospitalized with COVID-19 are associated with greater disease severity. Endocrine Practice, 26(8), 934-941.*

- Clinical study showing that vitamin D deficiency is associated with increased inflammation and greater severity of respiratory disease

✓ *Ulbricht, C., Basch, E., Cheung, L., et al. (2014) An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the Natural Standard Research Collaboration. Journal of Dietary Supplements, 11(1), 80-120.*

- Systematic review of elderberry’s anti-inflammatory, immunomodulatory, and clinical evidence, supporting its application in alleviating respiratory inflammation

✓ *Sorice, A., Guerriero, E., Capone, F., Colonna, G., Castello, G., & Costantini, S. (2014) Ascorbic acid: Its role in immune system and chronic inflammation diseases. Mini-Reviews in Medicinal Chemistry, 14(5), 444-452.*

- Reviews the role of vitamin C in antioxidation, inflammation regulation, and maintenance of immune function

✓ *Maares, M., & Haase, H. (2020) Zinc and immunity: An essential interrelation. Archives of Biochemistry and Biophysics, 611, 58-65.*

- Summarizes zinc’s essential role in immune homeostasis, inflammasome regulation, and attenuation of allergic responses

✓ *Hale, L. P., Greer, P. K., & Sempowski, G. D. (2005) Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clinical Immunology, 116(2), 135-142.*

- Provides experimental evidence that bromelain modulates leukocyte function, suppresses pro-inflammatory cytokines, and enhances anti-inflammatory feedback

✓ *Secor, E. R., Carson, W. F., Cloutier, M. M., Guernsey, L. A., Schramm, C. M., & Thrall, R. S. (2005) Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cellular Immunology, 237(1), 68-75.*

- Animal study showing that bromelain reduces allergic airway inflammation, decreases eosinophil infiltration, and mitigates airway hyperresponsiveness

II Axis II - Antioxidant and Barrier Homeostasis

In respiratory disease pathology, oxidative stress and barrier disruption represent common core problems across the acute, recovery, and chronic phases.

A. Central Role of Oxidative Stress

Infection and inflammatory activation rapidly induce macrophages and neutrophils to release large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These radicals exert a “double-edged sword” effect: within moderate limits they assist in pathogen clearance, but in excess they trigger cascading damage:

- Lipid peroxidation → disrupts cell and organelle membranes, undermining barrier integrity
- Protein carbonylation → inactivates functional proteins (enzymes, receptors, tight junction proteins), weakening cellular function
- DNA damage → induces apoptosis or necrosis, accelerating tissue injury

These processes not only exacerbate acute inflammation but also drive airway remodeling, fibrosis, and progressive functional decline in chronic stages.

B. Barrier Disruption and Increased Permeability

The epithelial and endothelial barriers of the respiratory tract are the first lines of defense against pathogen invasion and inflammatory spread. Under oxidative stress:

- Expression and conformation of tight junction proteins (occludin, claudin, ZO-1) are downregulated or disrupted
- Epithelial adhesion loosens, leading to increased barrier permeability
- Inflammatory mediators and pathogens penetrate more readily into deeper tissue layers

This damage fuels a vicious cycle of “infection-inflammation-injury-reinfection,” underlying recurrent and persistent respiratory disease.

C. Limitations of Anti-Inflammatory and Antiviral Interventions

Relying solely on antiviral or anti-inflammatory approaches often fails to break this cycle:

- Antivirals reduce pathogen load but cannot repair damaged barriers
- Anti-inflammatories lower inflammatory intensity but cannot prevent recurrent activation when barrier fragility persists

Thus, single-target strategies cannot provide full-cycle protection.

D. The Need for Antioxidant and Barrier Homeostasis

Nutritional interventions for respiratory health must simultaneously address antioxidant defense and barrier repair:

- Antioxidant defense → clears ROS/RNS, lowering inflammatory amplification and apoptosis
- Barrier homeostasis → regulates tight junction proteins and extracellular matrix (ECM) metabolism, reinforcing both physical and biochemical defenses

E. Positioning of Keyora LungOra 8 in 1

The second axis of Keyora LungOra 8 in 1 - Antioxidant and Barrier Homeostasis - is designed on this principle: constructing a systematic “antioxidant defense network and barrier repair system” to disrupt the vicious cycle of oxidative stress, inflammatory amplification, and barrier collapse, thereby providing protection across both acute and chronic phases.

- Vitamin C and quercetin → establish a complementary aqueous–lipid antioxidant core. Vitamin C eliminates ROS/RNS in the aqueous phase and supports collagen stability; quercetin prevents lipid peroxidation within membranes. Their regeneration cycle creates cross-phase synergy, amplifying overall antioxidant capacity.
- Elderberry polyphenols → broaden the antioxidant spectrum. Anthocyanins and polyphenols buffer sustained oxidative load in chronic inflammation, protecting against repeated barrier damage and supporting long-term stability in chronic respiratory disease.
- Zinc and vitamin D → cooperate to maintain epithelial and endothelial barrier homeostasis. Zinc stabilizes occludin and claudin expression and induces

metallothionein to lower ROS, while vitamin D via VDR signaling promotes epithelial repair and antimicrobial peptide secretion, strengthening barrier immune defense.

- Bromelain → beyond mucokinetic benefits, its anti-inflammatory and proteolytic activities reduce edema and exudation, relieve pressure on barrier structures, and clear necrotic cells and immune complexes - creating a low-inflammation environment for barrier restoration.
- Fish-derived elastin peptides → supply structural precursors rich in desmosine and isodesmosine for elastic fiber and basement membrane repair. In synergy with vitamin C, they drive collagen–elastin complex remodeling, enhancing barrier resilience and resistance to external insults.
- Mulberry leaf extract → serves as a “metabolic–inflammatory buffer.” By providing 1-DNJ to inhibit α-glucosidase, it lowers postprandial glucose spikes and AGE formation, reducing AGE–RAGE signaling and oxidative injury to barrier structures. Its polyphenols add further antioxidant support, sustaining barrier stability over the long term.

F. Conclusion

Axis II integrates antioxidant cores (vitamin C, quercetin, elderberry polyphenols, and mulberry leaf) with barrier-supporting agents (zinc, vitamin D, bromelain, fish elastin peptides) to achieve:

- Clearance of oxidative burden → lowering inflammatory triggers

- Reinforcement of physical barriers → enhanced epithelial and basement membrane integrity
- Promotion of structural repair → recovery of ECM and elastic fiber networks

The distinctiveness of this axis lies in not only buffering acute oxidative stress and barrier injury but also supporting structural reconstruction in chronic disease, thereby securing long-term functional stability of the respiratory system.

3) Module III - Antioxidant Defense and Barrier Integrity Maintenance

The preservation of respiratory health depends critically on two interconnected systems: a robust antioxidant defense network and the structural integrity of epithelial-endothelial barriers. Infections, chronic inflammation, and immune activation drive excessive production of reactive oxygen and nitrogen species (ROS/RNS).
While moderate levels of these species are important for microbial clearance, uncontrolled accumulation triggers a cascade of damage: lipid peroxidation undermines membrane stability, protein carbonylation inactivates key enzymes and junctional proteins, and oxidative DNA injury accelerates cell death and tissue destruction. Collectively, these processes amplify inflammation and predispose to chronic airway remodeling and fibrosis.

Barrier disruption is a downstream consequence of oxidative stress. Loss or dysfunction of tight junction proteins (occludin, claudin, ZO-1) loosens epithelial cohesion, raising

permeability and enabling deeper penetration of pathogens and inflammatory mediators. This breakdown perpetuates a vicious cycle of infection, inflammation, and tissue injury that underlies both acute exacerbations and chronic respiratory decline.

Relying solely on antiviral or anti-inflammatory interventions is insufficient to interrupt this cycle. Antiviral strategies can lower pathogen burden but cannot restore compromised barriers; anti-inflammatory approaches may reduce symptom intensity but fail to prevent recurrent barrier collapse. For this reason, integrated strategies that couple oxidative stress control with barrier stabilization are essential.

Keyora LungOra 8 in 1 was designed to target this dual requirement by assembling a coordinated antioxidant-barrier axis:

- **Vitamin C** acts as the central aqueous-phase antioxidant, rapidly neutralizing ROS/RNS and maintaining redox balance. As an indispensable cofactor for prolyl and lysyl hydroxylases, it also supports collagen maturation and basement membrane stability, directly reinforcing barrier resilience.
- **Quercetin** provides complementary lipid-phase protection, attenuating membrane lipid peroxidation and safeguarding mitochondrial integrity. It synergizes with vitamin C through a redox recycling mechanism, creating a cross-phase antioxidant network.
- **Elderberry polyphenols** broaden the antioxidant spectrum, particularly in chronic inflammatory states, where anthocyanins and polyphenols buffer sustained oxidative stress and reduce the frequency of barrier relapse.

- **Mulberry leaf extract** functions as a metabolic-inflammatory buffer by suppressing postprandial glucose spikes (via α-glucosidase inhibition) and thereby lowering AGE formation and secondary ROS production. Its intrinsic polyphenols further contribute to background antioxidant capacity, easing metabolic stress on epithelial barriers.
- **Zinc** stabilizes epithelial and endothelial junctions by regulating tight junction proteins, while metallothionein induction enhances free radical scavenging. This dual role secures barrier integrity under oxidative load.
- **Vitamin D** acts through VDR signaling to promote epithelial regeneration, enhance antimicrobial peptide expression, and reduce excessive inflammatory signaling, preventing secondary barrier injury.
- **Bromelain** complements these effects by reducing local edema and exudation, lowering mechanical stress on barrier tissues. Its proteolytic action clears necrotic debris and immune complexes, generating a microenvironment conducive to repair.
- **Fish cardiac bulb–derived elastin peptides** provide structural substrates - desmosine and isodesmosine - for elastic fiber and basement membrane reconstruction. In combination with vitamin C, they drive ECM remodeling and restore biomechanical resilience of the respiratory barrier.

Taken together, this antioxidant–barrier composite strategy ensures multi-layered protection:

- **Oxidative control**: vitamin C, quercetin, elderberry, mulberry, and zinc form a synergistic antioxidant network spanning aqueous, lipid, and metabolic compartments.
- **Barrier reinforcement**: vitamin D, bromelain, and elastin peptides rebuild epithelial and ECM structures, consolidating both physical and functional defenses.

The integrated outcome is a continuous protective pathway - limiting oxidative injury, preserving epithelial homeostasis, and promoting structural repair - that provides resilience across both acute infection and chronic disease trajectories.

3.1) Quercetin:

A Lipid-Phase Antioxidant Core and Barrier Protector

A. Lipid-phase antioxidant function and membrane protection

As a representative flavonoid polyphenol, quercetin exerts its greatest antioxidant advantage within lipid-rich domains of cellular and mitochondrial membranes.
By directly intercepting lipid peroxyl radicals (LOO•), it disrupts lipid peroxidation chain reactions and thereby:

- Preserves the integrity of cell and organelle membranes,
- Prevents abnormal increases in membrane fluidity, and
- Reduces epithelial barrier permeability, particularly in respiratory epithelial cells.

This lipid-phase protection complements the aqueous-phase activity of vitamin C, establishing a cross-compartmental antioxidant network.

B. Suppression of ROS-driven inflammatory amplification

Excessive ROS function not only as damaging agents but also as secondary messengers that activate NF-κB and p38 MAPK signaling cascades.

By quenching radicals within the lipid membrane compartment, quercetin lowers the threshold for ROS-triggered activation and indirectly prevents inflammatory amplification, thereby disrupting the vicious cycle between oxidative stress and inflammation.

C. Barrier structural protection

Beyond redox regulation, quercetin directly supports epithelial barrier integrity by modulating tight junction proteins:

- Enhancing the expression of occludin, claudin-1, and ZO-1,
- Stabilizing intercellular adhesion, and
- Limiting paracellular permeability.

In chronic inflammation models, quercetin supplementation has been shown to reduce alveolar leakage and edema, reflecting its barrier-protective capacity.

D. Synergistic interactions with other nutrients

- Vitamin C: Recycles oxidized quercetin back to its active form, prolonging its antioxidant lifespan through a redox regeneration loop.
- Elderberry polyphenols: Broaden the antioxidant spectrum, reinforcing quercetin's membrane-level activity.
- Zinc and vitamin D: Quercetin secures membrane and junctional integrity, while zinc and vitamin D facilitate structural repair, forming a "protection + repair" partnership.

E. Clinical applicability

Quercetin's lipid-phase antioxidant and barrier-stabilizing properties make it particularly valuable for:

- Acute respiratory infections: mitigating oxidative membrane injury, reducing barrier leakage, and lowering the risk of secondary infection,
- Chronic airway inflammation (e.g., COPD, asthma): decreasing barrier disruption and fluid extravasation, thereby improving airway stability,
- High oxidative-stress populations (smokers, elderly, metabolic dysfunction): functioning as a key lipid-phase antioxidant and barrier-protective agent.

3.2) Bromelain:

Microenvironment Modulation and Barrier Homeostasis Support

A. Attenuation of local inflammation and edema to relieve barrier stress

Oxidative stress in the respiratory tract is often accompanied by tissue exudation and localized edema, which increase the mechanical burden on epithelial barriers. Bromelain reduces these stressors by suppressing the release of COX-2, PGE_2, TNF-α, and IL-6, thereby:

- Diminishing inflammatory exudation and edema,
- Mitigating disruption of tight junction proteins, and
- Slowing the rate of barrier functional decline.

For airway mucosa, this translates into a more stable barrier environment and a lower risk of secondary infections.

B. Proteolytic clearance of necrotic debris and immune complexes

Through its proteolytic activity, bromelain helps remove necrotic cell fragments and immune complexes that accumulate during airway inflammation. This action:

- Reduces the deposition of inflammatory “debris” within the mucosa,
- Lowers immune-complex–driven chronic inflammation, and
- Provides a cleaner microenvironment that facilitates epithelial repair.

This function is particularly valuable in chronic airway conditions such as COPD and chronic bronchitis.

C. Creating a “low-inflammation” ecological niche for barrier repair

Although bromelain does not directly increase tight junction protein expression, it indirectly supports epithelial repair by reducing inflammatory resistance and edema.

- In synergy with vitamin D: vitamin D promotes epithelial regeneration, while bromelain reduces the inflammatory load that impedes repair.
- In synergy with fish cardiac bulb-derived elastin peptides: elastin peptides supply structural substrates for ECM remodeling, while bromelain maintains a low-inflammation milieu that supports effective integration.

D. Indirect antioxidant contribution

While not a classical antioxidant, bromelain decreases ROS production by limiting upstream inflammatory mediators, thus reducing oxidative burden. This indirectly supports the antioxidant network, easing the demand on agents such as vitamin C and quercetin.

E. Clinical applicability

- Acute inflammatory phase: reduces inflammatory exudation, preventing acute barrier collapse.
- Chronic inflammatory phase: clears immune complexes and necrotic debris, lowering the risk of long-term barrier deterioration.
- Structural repair phase: complements vitamin D and elastin peptides by aligning environmental modulation with structural rebuilding.

F. Summary

Bromelain's role within Module III can be summarized as:

- Relieving barrier stress by reducing inflammation and edema,
- Clearing the barrier environment via proteolytic removal of immune debris,
- Contributing indirect antioxidant benefits by limiting ROS sources, and
- Acting synergistically with vitamin D and elastin peptides to couple a low-inflammation environment with structural substrates for repair.

Positioned not as a primary antioxidant but as an "environmental modulator of barrier homeostasis," bromelain serves as a bridging factor in the antioxidant–repair chain, ensuring that structural protection and regeneration occur under stable inflammatory conditions.

3.3) Fish cardiac bulb-derived elastin peptides:

Structural Repair and Barrier Reconstruction

In respiratory disease recovery, anti-inflammatory, antioxidant, and antiviral strategies alone are insufficient for long-term stability; structural repair is the cornerstone of functional restoration. Acute inflammation and oxidative stress often cause alveolar and vascular elastic fibers to rupture, leading to impaired epithelial and endothelial barriers, reduced pulmonary compliance, increased permeability, and - in severe cases - irreversible fibrosis. Without effective extracellular matrix (ECM) repair, the body

frequently replaces damaged elastic fibers with low-quality collagen deposits, resulting in rigid rather than resilient tissue and ultimately compromising recovery quality.

Fish cardiac bulb-derived elastin peptides derived from arterial bulb elastin tissue, address this critical gap. They are naturally enriched in elastin-specific cross-linking amino acids such as desmosine and isodesmosine, which serve as direct substrates for elastin synthesis and network rebuilding. In synergy with cofactors such as vitamin C, Fish cardiac bulb-derived elastin peptides not only support ECM reconstitution but also restore the functional elasticity of the pulmonary network, reducing the risk of fibrosis and stiffening.

Accordingly, within the Module III framework of Keyora LungOra 8 in 1, Fish cardiac bulb-derived elastin peptides are positioned as a *primary driver of structural repair and barrier reconstruction*. Their inclusion ensures that the formulation extends beyond acute protection, providing deeper support for recovery and long-term management of respiratory function.

A. Supplying structural substrates for elastic network repair

a) The role of the collagen–elastin network in respiratory physiology

The architecture of the respiratory tract depends on the complementary properties of collagen and elastin fibers:

- Collagen fibers provide tensile strength, maintaining structural support for pulmonary tissue and vasculature.
- Elastin fibers confer stretchability and recoil, enabling alveoli to expand and contract effectively during the breathing cycle.

During acute inflammatory insults (e.g., viral pneumonia, ARDS) or chronic injury (e.g., COPD, asthma), elastin is degraded by proteases and oxidative stress. This breakdown results in the loss of desmosine and isodesmosine - signature amino acids critical for cross-linking and elasticity. The consequence is impaired alveolar recoil, diminished pulmonary compliance, and reduced efficiency of gas exchange.

b) Structural characteristics of Fish cardiac bulb-derived elastin peptides

Fish cardiac bulb-derived elastin peptides are derived from highly elastic cardiac bulb tissue and are distinguished by several unique features:

- They are rich in desmosine and isodesmosine, elastin-specific cross-linking amino acids that serve as molecular “fingerprints” of native elastin and are indispensable for the formation of functional cross-linking sites in elastic fibers.
- They contain small amino acid residues such as glycine, proline, and lysine, which act as substrates for elastin biosynthesis within the extracellular matrix (ECM).
- They retain naturally bioactive peptide fragments that have been shown in research to directly stimulate fibroblasts to synthesize new elastic fibers.

Thus, Fish cardiac bulb-derived elastin peptides are not merely a source of generic amino acid supplementation; they represent a targeted delivery of structural substrates, directly embedded into the ECM repair process during pulmonary tissue regeneration.

c) Synergy with vitamin C

The synthesis of both elastin and collagen requires hydroxylation of proline and lysine residues, a process that depends on vitamin C as a cofactor for hydroxylase enzymes.

- Fish cardiac bulb-derived elastin peptides supply the raw substrates: desmosine, isodesmosine, and proline residues.
- Vitamin C ensures the catalytic environment necessary for proper hydroxylation and stable cross-linking.

Together, they steer tissue repair away from low-quality fibrotic deposition and instead toward the formation of functional, extensible elastic networks. This synergy is critical to preventing pulmonary stiffening and irreversible loss of respiratory function.

d) Clinical implications: from patching defects to restoring function

Most tissue repair processes are dominated by collagen deposition, often resulting in rigid, non-extensible fibrotic tissue - analogous to scar formation - that perpetuates reduced pulmonary compliance.

The distinct value of Fish cardiac bulb-derived elastin peptides lies in their ability to:

- Not only “fill structural gaps” but also restore elastic properties of the repaired tissue.
- Enable repaired lung tissue to actively participate in normal respiratory dynamics.
- Improve the reversible stretch and recoil of alveoli and vasculature, thereby preventing long-term dyspnea and impaired gas exchange in the recovery phase.

In this sense, Fish cardiac bulb-derived elastin peptides move beyond structural repair to provide true functional restoration in respiratory recovery.

e) Summary

By supplying natural elastin cross-linking residues and matrix substrates - and working in synergy with vitamin C - Fish cardiac bulb-derived elastin peptides achieve the transition from barrier patching to functional recovery. This positions them as a pivotal nutritional intervention in the recovery phase of respiratory disease, supporting both the structural and functional rehabilitation of the pulmonary system.

B. Indirect Antioxidant and Matrix-Protective Effects

a) Vulnerability of elastin to oxidative stress

Elastin is a long-lived, slowly renewing extracellular matrix protein, and once oxidatively damaged, its structural impairment is largely irreversible. During airway inflammation or under conditions of heightened oxidative stress:

- Reactive oxygen and nitrogen species (ROS/RNS) attack proline and lysine residues within elastic fibers.
- The characteristic cross-linking amino acids, desmosine and isodesmosine, are highly susceptible to cleavage or oxidative inactivation.
- The consequence is disruption of the elastic network, manifesting as alveolar overexpansion (emphysema in COPD) or reduced tissue compliance.

These features make antioxidant protection especially critical for matrix integrity.

b) Buffering effects of Fish cardiac bulb-derived elastin peptides

Supplementation with Fish cardiac bulb-derived elastin peptides provides a dual protective benefit:

- As surrogate targets - supplying elastin-derived fragments that can absorb oxidative attack, thereby sparing native structural fibers from direct damage.
- As facilitators of regeneration - continuously providing cross-linking amino acids during matrix synthesis, enabling newly formed elastic fibers to rapidly compensate for injury.

In this way, Fish cardiac bulb-derived elastin peptides act as both a “sacrificial shield” and a “rebuilding catalyst,” simultaneously absorbing oxidative burden while accelerating structural reconstruction.

c) Synergy with the antioxidant network

Although Fish cardiac bulb-derived elastin peptides are not classical antioxidants, they complement the formula’s antioxidant constituents (vitamin C, quercetin, elderberry polyphenols):

- Vitamin C - lowers free radical burden in the aqueous phase, creating a low-oxidative environment conducive to elastin repair.
- Quercetin - stabilizes membranes in lipid compartments, reducing upstream ROS generation and indirectly safeguarding the matrix.
- Elderberry polyphenols - provide long-term buffering against oxidative load, mitigating chronic damage to structural proteins.
- Fish cardiac bulb-derived elastin peptides - integrate efficiently into the ECM under these favorable conditions, ensuring that repair proceeds without interruption.

This cooperative logic can be summarized as “antioxidant noise reduction + matrix reconstruction”: the former minimizes oxidative interference, while the latter secures structural renewal.

d) Clinical applicability

- Acute lung injury (e.g., viral pneumonia, ARDS): mitigates oxidative degradation of elastin, enhancing the likelihood of successful repair.

- Chronic obstructive pulmonary disease (COPD): slows progressive elastin degradation, attenuating emphysematous remodeling.
- Recovery and elderly populations: provides structural defense and functional support in contexts where oxidative stress and ECM breakdown coexist.

e) Summary

The role of Fish cardiac bulb-derived elastin peptides in Module III is not to directly scavenge free radicals but rather to preserve ECM integrity indirectly - by dispersing oxidative assault, supplying essential substrates for repair, and working synergistically with the antioxidant network.

This strategy ensures barrier reconstruction that is not only more stable but also more durable over time.

C. Enhancing the Compliance of Epithelial and Endothelial Barriers

a) Barrier function is not only about “sealing” but also about “dynamic regulation”

The airway barriers (epithelial and vascular endothelial layers) must both prevent the penetration of pathogens and inflammatory mediators, and at the same time remain flexible and compliant during respiratory movements and blood perfusion.

- Lack of elastin → barriers become rigid and prone to rupture

- Excessive collagen deposition → closes structural gaps but results in tissue stiffening and reduced gas exchange efficiency
- Optimal repair → stable, yet capable of extension and recoil

The value of fish cardiac bulb-derived elastin peptides lies in restoring this “functional barrier,” rather than providing a mere patch.

b) Improving the flexibility of the alveolar barrier

The alveolar wall relies on an “elastic fiber network” to support expansion and recoil during the respiratory cycle.

- Supplementation with fish cardiac bulb–derived elastin peptides provides elastin-specific cross-linking amino acids (desmosine and isodesmosine), which directly promote the reconstruction of functional elastic fibers
- In synergy with vitamin C, they ensure that fiber cross-links are stable yet not rigid
- The repair outcome is enhanced alveolar flexibility, restoration of gas-exchange surface area, and prevention of stiff scarring caused by excessive collagen deposition

c) Stabilizing the vascular endothelial barrier and reducing leakage

Respiratory diseases such as ARDS, severe pneumonia, and Post-COVID-19 Syndrome are often accompanied by endothelial barrier damage, resulting in leakage, pulmonary edema, and hypoxemia.

- Elastin is an essential structural element of the vascular basement membrane and medial layer, determining both elasticity and permeability control
- Fish cardiac bulb-derived elastin peptides promote the regeneration of elastic fibers, restoring endothelial compliance and reducing leakage of inflammatory mediators and fluid
- Clinically, this contributes to reduced pulmonary edema and improved oxygenation

d) Synergies with other components

- With vitamin D: vitamin D regulates epithelial proliferation and tight junction expression via VDR, while fish cardiac bulb-derived elastin peptides supply structural substrates - together providing “cellular regulation + matrix reconstruction”
- With bromelain: bromelain reduces inflammatory exudates and necrotic debris, creating a low-inflammation environment that allows elastin peptides to complete substantive ECM rebuilding
- With the antioxidant network (vitamin C, quercetin, elderberry polyphenols): antioxidants reduce ROS-mediated damage, ensuring the stability of newly formed elastic networks

e) Clinical applicability

- Acute lung injury: in ARDS or severe pneumonia recovery, reduces rigid scarring of alveolar and vascular barriers and enhances compliance
- Chronic airway disease: in COPD and asthma, improves barrier flexibility, alleviating recurrent airflow limitation and dyspnea
- Rehabilitation and aging populations: helps maintain elastic reserves of airways and vasculature, delaying functional decline

f) Summary

By reconstructing the elastic fiber network, fish cardiac bulb-derived elastin peptides shift repair from “rigid scarring” toward “flexible regeneration,” simultaneously reducing leakage and restoring dynamic compliance. This positions them as an indispensable structural nutritional support for the recovery phase of respiratory health.

D. Synergistic Logic with Other Nutrients

Fish cardiac bulb–derived elastin peptides do not act in isolation; their greatest value lies in fitting into a broader synergy of “structural repair” and “functional support.”
In combination with other nutrients in the formulation, they help create a closed-loop system of antioxidation, anti-inflammation, and tissue regeneration.

a) With vitamin C - “substrate + cofactor” pairing

- Fish cardiac bulb–derived elastin peptides supply the unique cross-linking amino acids (desmosine, isodesmosine) and elastin fragments required for ECM reconstruction
- Vitamin C, as the essential cofactor for prolyl and lysyl hydroxylases, ensures proper hydroxylation and cross-linking of these substrates
- Together, they guide ECM repair toward functional elastic networks rather than fibrotic substitution

Result: repaired tissues regain elasticity and extensibility rather than stiffening.

b) With vitamin D - “repair environment + repair substrate”

- Vitamin D, via VDR signaling, promotes epithelial differentiation, tight junction protein expression, and antimicrobial peptide production, establishing a regenerative environment
- Fish cardiac bulb–derived elastin peptides provide the structural building blocks required for ECM reconstruction
- This complementary model integrates “environment + substrate”

Result: epithelial, basement membrane, and ECM repair proceed holistically, avoiding superficial closure with deeper structural deficits left unresolved.

c) With bromelain - “low-inflammation background + structural rebuilding”

- Bromelain clears necrotic debris and immune complexes, reducing local inflammation and edema
- Fish cardiac bulb–derived elastin peptides embed efficiently into the ECM within this low-inflammation environment, completing effective reconstruction
- The two together prevent inflammation-driven fibrotic remodeling

Result: higher-quality repair with reduced risk of pulmonary fibrosis.

d) With the antioxidant network (quercetin, elderberry polyphenols, vitamin C, zinc)

- Antioxidants clear ROS, reducing oxidative damage to newly synthesized ECM
- Zinc stabilizes tight junction proteins and lowers barrier permeability
- Within this framework, fish cardiac bulb–derived elastin peptides function as the “builder,” converting the low-stress environment created by antioxidants into sustainable structural repair

Result: seamless transition from oxidative protection to structural rehabilitation.

e) Position within the overall formulation

- Immune and antiviral axis (Module I): limits pathogen invasion and replication
- Inflammation and antioxidation (Modules II & early Module III): suppresses inflammation, clears free radicals

- Structural repair (late Module III): led by fish cardiac bulb–derived elastin peptides, enabling true functional restoration

As the only component that directly provides structural rebuilding capacity, they determine the depth and durability of recovery.

f) Summary

By working synergistically with vitamin C, vitamin D, bromelain, and the antioxidant network, fish cardiac bulb–derived elastin peptides transform a “low-inflammation, low-oxidative” milieu into high-quality structural regeneration.

This allows Keyora LungOra 8 in 1 not only to alleviate symptoms but also to restore damaged elastic connective tissues, driving genuine respiratory recovery.

E. Clinical Applicability and Rehabilitative Value

a) Recovery phase following acute lung injury

In conditions such as viral pneumonia, ARDS, and severe COVID-19, the post-acute phase is characterized by elastic fiber rupture, barrier leakage, and risk of fibrotic remodeling.

- Supplementation with fish cardiac bulb–derived elastin peptides provides the essential cross-linking amino acids required for elastic network reconstruction

- In synergy with vitamin C and vitamin D, these peptides enhance the quality of repair, steering tissue remodeling away from collagen-dominated fibrosis
- The outcome is improved pulmonary compliance, reduced pulmonary edema, and better oxygenation

Clinical value: helps patients recovering from acute injury avoid “rigid scarring” and lowers the risk of long-term respiratory insufficiency.

b) Chronic obstructive pulmonary disease (COPD) and asthma

In COPD, chronic bronchitis, and asthma, persistent inflammation and protease activity degrade elastic fibers, driving emphysema, airway remodeling, and breathlessness.

- Fish cardiac bulb-derived elastin peptides slow ongoing elastin degradation and act as direct substrates for matrix repair, stabilizing alveolar structure
- In combination with bromelain, they reduce immune complex deposition and attenuate fibrotic remodeling
- This synergy improves long-term respiratory endurance and exercise capacity

Clinical value: serves as structural nutritional support in chronic disease management, slowing progression of structural decline.

c) Rehabilitation and aging populations

Elderly individuals, post-surgical patients, and those chronically exposed to high-risk factors (e.g., smoking, dust, air pollution) often experience elevated oxidative stress, rapid ECM degradation, and impaired repair capacity.

- Fish cardiac bulb-derived elastin peptides provide direct structural matrix support in these populations
- In conjunction with the antioxidant network (vitamin C, quercetin, elderberry), they mitigate ECM damage
- In synergy with vitamin D and zinc, they reinforce barrier repair and immune homeostasis

Clinical value: enhances rehabilitation quality, slows age-related respiratory decline, and improves quality of life and endurance.

d) Summary of applicability

- Post-acute recovery → restores pulmonary compliance, prevents fibrosis
- Chronic obstructive diseases → delays structural deterioration, improves functional endurance
- High-risk and elderly populations → provides structural nutritional support, mitigates functional decline

e) Conclusion

The principal clinical value of fish cardiac bulb-derived elastin peptides lies in their ability to connect acute protection, recovery-phase repair, and long-term maintenance into a coherent continuum. They ensure that recovery extends beyond symptom control to achieve sustained structural and functional stability of the respiratory system.

F. Summary of Fish Cardiac Bulb–Derived Elastin Peptides

Within the second axis of Keyora LungOra 8 in 1 (Antioxidant–Barrier Homeostasis Axis), fish cardiac bulb-derived elastin peptides serve as an irreplaceable structural repair factor. Their unique value lies not only in providing the “terminal repair” that follows antioxidant defense, but also in determining whether recovery advances toward true functional restoration rather than rigid scarring.

Provision of structural substrates for elastic network repair

By supplying the characteristic cross-linking amino acids desmosine and isodesmosine, these peptides directly participate in elastin fiber reconstruction. In the presence of vitamin C as an enzymatic cofactor, they guide repair toward functional elastic networks rather than fibrotic scar tissue.

Indirect effects in antioxidant buffering and matrix protection

In high-oxidative environments, they act as “sacrificial targets” that buffer free radical attacks while simultaneously accelerating ECM regeneration. In synergy with vitamin C,

quercetin, and elderberry polyphenols, they synchronize antioxidant defense with structural rebuilding.

Enhancement of epithelial and endothelial compliance

By restoring elasticity to alveolar and vascular walls, these peptides ensure that barriers not only close breaches but also retain flexibility. This reduces leakage and edema, thereby improving gas-exchange efficiency.

Synergistic interactions with other nutrients

- With vitamin C → “substrate + cofactor” synergy ensures high-quality ECM repair
- With vitamin D → “repair environment + repair substrate” forms a complete regenerative chain
- With bromelain → high-quality elastin network rebuilding is achieved under a low-inflammatory background
- With the antioxidant network → structural reconstruction proceeds effectively under reduced oxidative stress

Clinical applicability and rehabilitative value

- Post–acute lung injury → prevents fibrotic remodeling and restores pulmonary compliance
- Chronic obstructive diseases → slows elastin degradation and improves endurance

- Rehabilitation and aging populations → provides structural nutritional support to sustain long-term respiratory function

In summary, fish cardiac bulb-derived elastin peptides are not only the cornerstone of structural repair but also the determinant of recovery quality.

Through five interconnected pathways - substrate supplementation, antioxidant protection, compliance restoration, nutrient synergy, and clinical rehabilitation - they bridge antioxidant defense with tissue reconstruction, enabling the respiratory system to transition from acute injury toward long-term stability and health.

3.4) Elderberry:

Broad-Spectrum Polyphenolic Antioxidant and Barrier Protection

A. Antioxidant roles of polyphenols and anthocyanins

Elderberry is rich in anthocyanins, flavonoids, and other polyphenols that mitigate oxidative stress through multiple mechanisms:

- Free radical scavenging – anthocyanins neutralize superoxide anions, hydroxyl radicals, and hydrogen peroxide.
- Iron chelation – reduces Fenton reaction–driven ROS production at its source.
- Inhibition of lipid peroxidation – protects cellular and mitochondrial membranes, preventing barrier fragility caused by structural damage.

This function is particularly important under conditions of chronic oxidative load, where it reduces inflammation-driven amplification and tissue injury.

B. Support for barrier homeostasis

Oxidative stress promotes degradation of tight junction proteins (occludin, claudin, ZO-1), increasing epithelial and endothelial permeability. Elderberry polyphenols:

- Attenuate ROS and inflammatory mediator levels, indirectly stabilizing tight junction protein expression.
- Improve endothelial function, limiting vascular leakage and alveolar fluid accumulation.
- Enhance airway epithelial defense, reducing the risk of secondary infections.

  Here, elderberry does not “repair” the barrier directly but maintains its stability by buffering oxidative and inflammatory pressures.

C. Complementarity with other antioxidants

Within the antioxidant network, elderberry polyphenols complement vitamin C, quercetin, and zinc:

- With vitamin C – oxidized anthocyanins are regenerated by vitamin C, prolonging their antioxidant lifespan.

- With quercetin – the two cover different redox niches, quercetin acting mainly in lipid phases and elderberry at aqueous–membrane interfaces.
- With zinc – elderberry reduces oxidative stress, while zinc stabilizes tight junction proteins, jointly supporting barrier integrity.

D. Significance of long-term antioxidant buffering

Unlike fast-acting antioxidants such as vitamin C, elderberry polyphenols have slower metabolism and longer half-lives, providing a “long-tail” antioxidant effect. This sustained protection is particularly suitable for:

- COPD and asthma patients – reduces chronic oxidative stress and barrier degradation.
- Elderly individuals – delays cumulative oxidative injury to respiratory function.
- High-risk groups (smokers, those exposed to air pollution) – provides additional antioxidant shielding.

E. Clinical applicability

Clinical studies show elderberry preparations shorten the course of influenza and upper respiratory tract infections, alleviating fever, sore throat, and nasal congestion. These effects are attributed not only to antiviral actions but also to reductions in oxidative stress and barrier leakage.

- Acute phase – alleviates oxidative stress and limits barrier permeability.
- Chronic phase – buffers low-grade oxidative inflammation, sustaining barrier stability.

F. Summary

The value of elderberry in *Module III* can be summarized as follows:

- Antioxidant coverage – scavenges free radicals, chelates iron, and suppresses lipid peroxidation.
- Barrier stabilization – indirectly maintains tight junction integrity and reduces leakage.
- Complementary synergy – works with vitamin C, quercetin, and zinc to broaden antioxidant defense.
- Sustained buffering – provides long-tail antioxidant protection, particularly suited for chronic conditions and aging populations.

Elderberry is not a high-intensity antioxidant per se but rather an expansion agent of the antioxidant spectrum, contributing long-term, buffering, and complementary effects within the formulation.

3.5) Mulberry Leaf:

Metabolic Homeostasis–Driven Barrier Protection

In respiratory diseases, the metabolic background often dictates the extent of oxidative stress and barrier injury.

Hyperglycemia and its downstream products - advanced glycation end products (AGEs) - not only generate free radicals directly but also amplify NF-κB and MAPK signaling through the AGE–RAGE axis, accelerating epithelial and endothelial barrier disruption. This cascade drives degradation of tight junction proteins and perpetuates inflammatory signaling, resulting in profound barrier dysfunction and chronic injury.

Mulberry leaf extract, owing to its unique 1-deoxynojirimycin (1-DNJ) content, inhibits α-glucosidase, thereby lowering postprandial glucose peaks and reducing AGE formation. Within the context of respiratory nutritional support, this means it can attenuate oxidative and inflammatory drivers from the metabolic source, alleviating chronic stress on the barrier.

Additionally, its polyphenols and flavonoids exert direct antioxidant effects, complementing the broader antioxidant network and strengthening barrier resilience against external insults.

Thus, in the framework of *Module III*, mulberry leaf extract functions as a regulator of the metabolic–oxidative background. Rather than repairing the barrier directly, it ensures stability and regeneration by controlling metabolism and lowering chronic oxidative burden.

A. Reduction of postprandial glucose fluctuations and oxidative load

- Postprandial hyperglycemia induces excessive ROS and RNS generation, weakening intrinsic antioxidant defenses.
- 1-DNJ in mulberry leaf inhibits α-glucosidase, delaying carbohydrate digestion and absorption.
- By blunting postprandial glucose spikes, it reduces oxidative stress stemming from glucose autoxidation and polyol pathway activation.

Significance: Relieves the acute oxidative burden on respiratory barriers, providing “front-end load reduction” for the antioxidant defense system.

B. Inhibition of the AGE–RAGE axis and inflammatory amplification

- Hyperglycemia accelerates AGE formation.
- AGE–RAGE binding activates NF-κB and MAPK signaling, amplifying inflammation and driving degradation of tight junction proteins.
- Mulberry leaf extract reduces AGE generation, thereby indirectly suppressing RAGE-mediated oxidative and inflammatory cascades.

Significance: Interrupts the vicious cycle of “metabolism → inflammation → barrier injury,” delaying barrier collapse.

C. Polyphenolic antioxidant effects and membrane protection

- Rich in flavonoids and polyphenols, mulberry leaf exhibits direct radical-scavenging activity.
- Complements vitamin C and quercetin to expand the antioxidant network, covering diverse radical species.
- In chronic inflammation, it protects membrane lipids from peroxidation, preventing repeated barrier damage.

Significance: Provides sustained antioxidant protection, particularly valuable for chronic respiratory disease management.

D. Synergistic roles

- With vitamin C, quercetin, and elderberry: forms a “multi-phase + long-tail” antioxidant spectrum.
- With zinc and vitamin D: provides a reduced metabolic stress background, facilitating tight junction stabilization and barrier repair.
- With fish cardiac bulb–derived elastin peptides: reduces AGE–RAGE–driven ECM damage, ensuring structural repair occurs under low-inflammatory, low-oxidative conditions.

Summary:

Within *Module III*, mulberry leaf extract acts as the background stabilizer of the metabolism–oxidation axis. By controlling blood glucose excursions, suppressing AGE–

RAGE signaling, and providing polyphenolic antioxidant activity, it systematically reduces the oxidative and inflammatory burden on respiratory barriers. This “back-end protection” creates the necessary conditions for barrier stability and regeneration.

3.6) Zinc:

A Key Trace Element for Tight Junction Stability and the Antioxidant Barrier

A. Regulator of Tight Junction Proteins

The integrity of respiratory epithelial and vascular endothelial barriers relies heavily on tight junction proteins such as occludin, claudin, and ZO-1. Zinc deficiency leads to:

- Reduced expression of these proteins, resulting in increased barrier permeability
- Easier penetration of pathogens and inflammatory mediators, aggravating infection and inflammation

Adequate zinc intake upregulates the expression and conformational stability of tight junction proteins, thereby directly reinforcing the physical robustness of the barrier.

B. Indirect Antioxidant Effects

Although zinc is not a direct radical scavenger, it exerts antioxidant functions through metallothioneins, which are zinc-inducible proteins rich in thiol groups:

- Metallothioneins bind and neutralize ROS as well as excess transition metals

- By eliminating triggers of oxidative chain reactions, they reduce damage to the ECM and barrier proteins
- Under chronic inflammation, zinc helps sustain a low-oxidative background conducive to tissue stability

C. Support for Epithelial Repair and Regeneration

As a cofactor for numerous enzymes and transcription factors - including DNA polymerases - zinc is indispensable for epithelial regeneration:

- Promotes epithelial cell proliferation and differentiation, accelerating barrier recovery
- Acts synergistically with vitamin D to improve repair quality
- Prevents incomplete or fragile barrier restoration that may occur in states of zinc insufficiency

D. Synergy within the Antioxidant Network

- With vitamin C: Vitamin C lowers ROS levels, while zinc-induced metallothioneins further buffer oxidative cascades
- With quercetin: Quercetin functions as a zinc ionophore, facilitating zinc entry into cells and amplifying its antioxidant and barrier-stabilizing effects
- With elderberry polyphenols: Adds broader antioxidant coverage, reducing persistent oxidative load in barrier environments

E. Clinical Applicability

- Acute phase: Zinc supplementation reduces post-infection barrier disruption and may shorten disease duration
- Chronic phase: In COPD and asthma, zinc status correlates positively with lung function and inversely with inflammatory markers
- Vulnerable and elderly populations: Maintains barrier stability and reduces susceptibility to infections and relapses

F. Summary

Zinc's role within *Module III* can be summarized across three pillars:

- Barrier stabilization – upregulation of tight junction proteins to lower permeability
- Indirect antioxidant defense – metallothionein-mediated buffering of ROS
- Repair support – facilitation of epithelial regeneration and restoration of barrier integrity

Within Keyora LungOra 8 in 1, zinc integrates with vitamin C, quercetin, elderberry, and vitamin D to form a cohesive antioxidant–barrier repair network, delivering subtle yet indispensable support for the long-term stability of respiratory barriers.

3.7) Vitamin D:

A Homeostatic Regulator of Epithelial Repair and Barrier Immunity

A. Epithelial Repair and Regeneration

The respiratory epithelium constitutes the body’s first line of defense. When epithelial repair is incomplete, barrier permeability remains chronically elevated.

- Vitamin D activates the vitamin D receptor (VDR) pathway, promoting epithelial cell proliferation, differentiation, and migration
- Upregulates tight junction proteins (occludin, claudin, ZO-1), directly enhancing barrier sealing capacity
- Acts synergistically with zinc, ensuring that repair is not only rapid but also functionally stable

Clinical relevance: Shortens the epithelial repair timeline and reduces the risk of secondary infections.

B. Antimicrobial Peptide Induction and Mucosal Defense

Vitamin D stimulates the expression of antimicrobial peptides such as LL-37 and β-defensins:

- Directly neutralizes bacteria and viruses, reducing pathogen pressure on the epithelial barrier
- Enhances the mucosal immune environment, making regenerating epithelial cells less vulnerable to reinfection

- Works together with vitamin C and quercetin to form a multi-layered antioxidant–anti-inflammatory–antimicrobial shield

C. Indirect Regulation of Oxidative Stress and Inflammation

Through activation of the Nrf2 pathway, vitamin D enhances intracellular antioxidant enzyme expression (SOD, CAT, GPx), thereby reducing ROS accumulation.

- Concurrently, vitamin D suppresses NF-κB activation and promotes autophagy, lowering inflammatory tone
- This creates a low-inflammatory, low-oxidative environment essential for ECM repair
- Synergizes with fish cardiac bulb–derived elastin peptides and bromelain, ensuring that matrix repair proceeds without secondary damage

D. Modulation of Immune Polarization and Tolerance

Chronic inflammation is often sustained by maladaptive immune polarization. Vitamin D helps rebalance this state:

- Downregulates Th1/Th17 pro-inflammatory responses
- Enhances Treg activity, fostering immune tolerance
- Prevents “inflammation-driven interference” during the barrier healing process

E. Clinical Applicability

- Post-acute lung injury: Accelerates epithelial repair and lowers reinfection risk
- Chronic airway inflammation (COPD, asthma): Improves barrier integrity and reduces chronic inflammatory load
- Elderly and vitamin D–deficient populations: Strengthens respiratory barrier defense and shortens recovery trajectories

E. Summary

Within Module III, vitamin D functions as a multidimensional stabilizer of epithelial and immune homeostasis:

- Repair: Drives epithelial regeneration and tight junction protein expression
- Defense: Boosts antimicrobial peptide production, reinforcing mucosal immunity
- Environmental optimization: Lowers oxidative stress and reshapes immune polarization, creating conditions favorable for ECM repair

Its unique contribution lies not merely in patching barrier gaps, but in ensuring that repair is functionally complete and immunologically balanced - making it the essential bridge between antioxidant protection and structural regeneration.

3.8) Vitamin C:

The Core Aqueous-Phase Antioxidant and a Collagen-Stabilizing Factor

A. Central Role in Aqueous-Phase Antioxidant Defense

Vitamin C is the dominant water-soluble antioxidant in the respiratory tract, present at high concentrations in the cytosol, plasma, and alveolar fluid.

- Rapidly neutralizes superoxide anions, hydroxyl radicals, and hydrogen peroxide
- Terminates radical chain reactions, thereby preventing secondary damage to DNA, proteins, and cell membranes
- During acute infection and inflammation, suppresses ROS surges that otherwise amplify inflammatory cascades

Function: Establishes the first line of antioxidant defense and lowers the oxidative stress threshold.

B. Collagen and Basement Membrane Stabilization

Vitamin C serves as an indispensable cofactor for prolyl and lysyl hydroxylases, enzymes that drive the hydroxylation and cross-linking of collagen and elastin.

- Deficiency destabilizes collagen chains, making basement membranes and vascular walls more fragile
- Adequate supply ensures strong collagen fibers and stable basement membranes, reducing barrier permeability
- Works synergistically with fish cardiac bulb–derived elastin peptides, which provide structural substrates, while vitamin C ensures efficient hydroxylation and cross-linking

Function: Reinforces barrier resilience and mechanical strength at the molecular level.

C. Regeneration of Other Antioxidants and Network Synergy

Vitamin C is not only a direct antioxidant but also a key regenerator of oxidized antioxidants:

- Restores quercetin, elderberry polyphenols, and other flavonoids to their active states, extending their antioxidant lifespan
- Participates in the ascorbate–glutathione–vitamin E cycle, covering aqueous, lipid, and membrane-interface phases of antioxidant defense

Function: Prolongs and broadens the antioxidant effect, preventing a “spike-then-decline” dynamic.

D. Indirect Support of Barrier Function

By dampening ROS and inflammatory mediators, vitamin C contributes to barrier integrity:

- Stabilizes tight junction protein expression, maintaining low epithelial permeability
- Improves microvascular endothelial function, reducing leakage and pulmonary edema
- Complements the barrier-repair effects of vitamin D and zinc

E. Clinical Applicability

- Acute respiratory infections: Shortens illness duration and reduces oxidative-inflammatory tissue damage
- ARDS and severe pneumonia: Attenuates oxidative stress and improves oxygenation
- Chronic airway diseases: Buffers long-term oxidative load, slowing barrier deterioration
- High-risk and elderly populations: Enhances structural resilience of barriers, reducing recurrent infections

F. Summary

Within *Module III*, vitamin C stands as the core aqueous-phase antioxidant with multi-tiered contributions:

- Rapid antioxidant defense: Neutralizes free radicals and dampens oxidative triggers
- Structural protection: Supports stable cross-linking of collagen and elastin
- Network synergy: Regenerates polyphenols (quercetin, elderberry) and other antioxidants
- Barrier support: Sustains tight junction and basement membrane integrity

Together with fish cardiac bulb-derived elastin peptides, vitamin C closes the "protect-and-repair loop": vitamin C provides a low-oxidative environment, while elastin peptides deliver structural substrates for high-quality barrier regeneration.

3.9) Module III - Integrated Summary:

Antioxidant Defense and Barrier Integrity Maintenance

Respiratory health depends not only on antiviral and anti-inflammatory defense but also on the ability to resist oxidative damage and preserve barrier integrity.

During both acute and chronic inflammation, excess ROS and RNS trigger lipid peroxidation, degradation of tight junction proteins, and extracellular matrix (ECM) breakdown. These changes increase barrier permeability, promote leakage, and heighten susceptibility to secondary infection.

Module III is designed to disrupt the "oxidative stress-inflammation-barrier collapse" cycle by building a synergistic nutrient network that drives both protection and repair.

A. Antioxidant Network

- Vitamin C – Core aqueous-phase antioxidant; rapidly neutralizes radicals, stabilizes collagen, and regenerates quercetin and elderberry polyphenols to sustain long-term antioxidant activity
- Quercetin – Lipid-phase antioxidant that halts lipid peroxidation chain reactions, preserves membrane integrity, and couples with vitamin C in regeneration cycles

- Elderberry polyphenols – Provide long-tail antioxidant buffering, particularly under chronic oxidative stress, broadening the spectrum of oxidative protection
- Zinc – Indirectly clears ROS via metallothionein induction, complementing vitamin C and quercetin in maintaining a low-oxidative background

B. Barrier Homeostasis and Repair

- Vitamin D – Activates VDR signaling to promote epithelial regeneration and tight junction expression, while inducing antimicrobial peptides to enhance barrier immunity
- Zinc – Directly stabilizes tight junction proteins, lowers barrier permeability, and supports epithelial repair
- Bromelain – Through anti-inflammatory and proteolytic effects, reduces exudate and necrotic debris, creating a low-inflammation environment for effective repair
- Fish cardiac bulb–derived elastin peptides – Supply structural amino acids (desmosine and isodesmosine) essential for elastin network rebuilding; in synergy with vitamin C, enable high-quality ECM reconstruction and restore barrier flexibility and functionality

C. Closed-Loop Logic

Module III establishes a multilayered closed-loop of "antioxidant defense-barrier stabilization-structural repair":

- Antioxidant clearance – Vitamin C, quercetin, elderberry, and zinc reduce oxidative burden
- Barrier stabilization – Vitamin D and zinc directly preserve tight junctions and epithelial integrity
- Repair promotion – Bromelain lowers inflammatory obstacles, while fish cardiac bulb–derived elastin peptides deliver structural rebuilding
- Synergistic complementarity – From environmental optimization to structural material provision, each nutrient interlocks with the next, ensuring that repair is not only rapid but also high-quality

D. Clinical Implications

- Acute phase: Limits oxidative damage and barrier collapse, alleviating symptom severity
- Recovery phase: Accelerates ECM and barrier regeneration, reducing the risk of fibrotic remodeling
- Chronic phase and aging populations: Buffers long-term oxidative stress, delays structural decline, and sustains respiratory function over time

E. Conclusion:

Module III, through the coordinated action of eight nutrients, achieves a full-chain protective continuum - from radical scavenging, to barrier stabilization, to elastin network

reconstruction.

This module represents the core value of Keyora LungOra 8 in 1 within the Antioxidant–Barrier Homeostasis Axis, linking acute protection with long-term functional resilience.

- ✓ *Carr, A. C., & Maggini, S. (2017) Vitamin C and immune function. Nutrients, 9(11), 1211.*

  - Discusses the role of vitamin C in immunity and antioxidant defense, highlighting its importance in respiratory barrier protection and collagen stability

- ✓ *Dorsch, W., Ring, J., & Bayer, T. (1984) Antiinflammatory actions of flavonoids and some of their metabolites. Allergology International, 33(4), 231-238.*

  - Explains the antioxidant and membrane-protective effects of flavonoids such as quercetin, supporting its role in lipid-phase antioxidation and barrier maintenance within Module III

- ✓ *Ulbricht, C., Basch, E., Cheung, L., et al. (2014) An evidence-based systematic review of elderberry and elderflower (Sambucus nigra). Journal of Dietary Supplements, 11(1), 80-120.*

  - Systematic review of elderberry’s antioxidant and anti-inflammatory properties, with particular emphasis on anthocyanins in barrier protection

- ✓ *Maares, M., & Haase, H. (2020) Zinc and immunity: An essential interrelation. Archives of Biochemistry and Biophysics, 611, 58-65.*

  - Summarizes zinc’s central role in immunity and barrier maintenance, including tight junction regulation and metallothionein-mediated antioxidant mechanisms

- ✓ *Greiller, C. L., & Martineau, A. R. (2015) Modulation of the immune response to respiratory viruses by vitamin D. Nutrients, 7(6), 4240-4270.*

- Demonstrates how vitamin D improves respiratory barrier function through epithelial repair, antimicrobial peptide secretion, and antioxidant pathways

✓ *Hale, L. P., Greer, P. K., & Sempowski, G. D. (2005) Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clinical Immunology, 116(2), 135-142.*

- Experimental evidence that bromelain reduces inflammatory exudation and edema, supporting its role in barrier protection and low-inflammation repair

✓ *Robert, L., Jacob, M. P., Frances, C., Godeau, G., & Hornebeck, W. (1984) Interaction between elastin and elastases and its role in the aging of the arterial wall. American Journal of Physiology, 247(4), H595-H602.*

- Describes the importance of elastin structural damage and repair, supporting the role of fish cardiac bulb–derived elastin peptides in barrier reconstruction

✓ *Shapiro, S. D., Endicott, S. K., Province, M. A., Pierce, J. A., & Campbell, E. J. (1991) Marked longevity of human lung parenchymal elastic fibers and contributions of elastase to lung destruction in smokers. Journal of Clinical Investigation, 87(5), 1828-1839.*

- Demonstrates that elastic fibers are long-lived yet highly vulnerable to degradation, underscoring the importance of supplying structural substrates for long-term lung tissue repair

III Axis III – Ventilation-Structure-Metabolism Axis

In the progression and recovery of respiratory diseases, beyond viral clearance, inflammation control, and oxidative stress reduction, a critical dimension lies in the restoration of ventilation and the preservation of structural integrity.

- **Acute phase:** Excessive mucus secretion and ciliary dysfunction can obstruct the airways, directly impairing oxygenation and ventilation efficiency.
- **Chronic phase:** If alveolar and airway structural damage is not adequately repaired, collagen deposition and fibrosis often replace the normal elastic network, ultimately leading to reduced lung compliance and impaired gas exchange.
- **Systemic dimension:** Chronic inflammation and oxidative stress extend beyond the respiratory tract, affecting metabolism and systemic homeostasis, thereby creating a vicious cycle of “local-to-systemic” injury.

Thus, recovery is not limited to “inflammation control” and “oxidative buffering”; it must also involve ventilation improvement, structural repair, and mitigation of metabolic–inflammatory coupling to achieve comprehensive restoration of respiratory function.

The design of ***Axis III*** (Ventilation-Structure-Metabolism Axis) in *Keyora LungOra 8 in 1* follows this integrative logic:

- **Module IV** – Mucociliary Dynamics and Ventilation Enhancement
- **Module V** – Structural Repair and Elastic Network Reconstruction
- **Module VI** – Metabolic-Inflammatory Coupling and Systemic “Noise Reduction”

Through this structured framework, the formula supports long-term respiratory health across three interlinked dimensions: airway clearance, alveolar elasticity, and systemic homeostasis.

4) Module IV – Mucociliary Dynamics and Ventilation Improvement

Airway mucus and ciliary activity represent the first-line defense of the respiratory system, yet during inflammation and infection, mucus often becomes overproduced, excessively viscous, and poorly cleared.

- Such abnormalities in mucociliary dynamics lead to mucus retention, airway obstruction, and impaired gas exchange.
- This, in turn, worsens hypoxemia and carbon dioxide retention, triggering dyspnea and secondary infections.
- In chronic conditions such as COPD, bronchitis, and asthma, these disturbances can create a vicious cycle of recurrent exacerbations.

Within Module IV, the nutritional design of Keyora LungOra 8 in 1 aims to restore airway dynamics through multi-pronged strategies of anti-inflammation, mucoregulation, and ciliary function enhancement:

- Bromelain – via proteolytic activity, reduces mucus viscosity and minimizes exudate deposition.

- Elderberry and quercetin – suppress inflammation-driven mucus hypersecretion, maintaining secretion within physiological range.
- Vitamin C and zinc – improve ciliary function and local immune defense, accelerating airway clearance.
- Fish cardiac bulb–derived elastin peptides – support deeper structural repair, enhancing airway compliance and reducing airflow resistance.
- Vitamin D – promotes epithelial differentiation and repair of the ciliated epithelium, while inducing antimicrobial peptides (LL-37, β-defensin) to lower the risk of secondary infections.
- Mulberry leaf extract – mitigates hypersecretion of mucus and airway inflammation under hyperglycemic conditions; its polyphenols further alleviate oxidative damage to ciliary function.

Core value of Module IV: by following the three-step logic of “mucus reduction – anti-inflammation – enhanced clearance,” it improves airway patency and ventilation efficiency, thereby relieving acute symptoms and supporting long-term respiratory quality.

4.1) Quercetin:

Suppression of Mucus Hypersecretion and Improvement of Airway Dynamics

A. Inhibition of Inflammation-Driven Mucus Secretion

Airway inflammation often activates signaling pathways such as EGFR, NF-κB, and MAPK, which induce overexpression of mucin genes (MUC5AC, MUC5B), resulting in viscous sputum and impaired clearance.

- Quercetin downregulates EGFR and NF-κB activity, thereby reducing MUC5AC expression.
- It suppresses mucus cell metaplasia driven by pro-inflammatory cytokines such as IL-13 and TNF-α.
- The outcome is reduced mucus output with a more normalized composition.

Effect: lowers mucus viscosity and decreases airway obstruction.

B. Enhancement of Ciliary Function

Ciliary motion is essential for mucus clearance, yet inflammation and oxidative stress can impair ciliary structure and rhythm.

- Quercetin mitigates ROS and inflammatory mediator levels, protecting ciliary integrity and rhythmicity.
- In vitro studies indicate that quercetin can increase ATP levels in airway epithelial cells, indirectly promoting ciliary beating.
- In synergy with vitamin C, it strengthens mucociliary clearance efficiency.

Effect: facilitates mucus–ciliary clearance and maintains airway patency.

C. Indirect Anti-Allergic and Anti-Inflammatory Effects

In asthma and allergic airway inflammation, histamine and leukotrienes stimulate mucus hypersecretion.

- Quercetin stabilizes mast cells, reducing histamine and leukotriene release.
- It decreases eosinophil infiltration, preventing chronic mucus overproduction.
- Under chronic airway inflammation, it exerts dual roles of “anti-allergy and mucus reduction.”

Effect: particularly suitable for conditions such as asthma and allergic rhinitis characterized by mucus hypersecretion.

D. Synergy with Other Components

- With bromelain: quercetin reduces mucus production, while bromelain directly lowers sputum viscosity, forming a complementary “reduction + dilution” mechanism.
- With vitamin C: vitamin C regenerates quercetin, prolonging its anti-inflammatory and mucus-suppressing effects.
- With elderberry: both downregulate inflammatory signaling, reducing chronic-phase mucus accumulation.

E. Clinical Applicability

- Acute respiratory infections: alleviates excessive sputum and obstruction, improving ventilation efficiency.
- Chronic bronchitis and COPD: suppresses long-term mucus cell metaplasia, easing dyspnea.
- Asthma and allergic rhinitis: mitigates allergy-induced hypersecretion, lowering symptom frequency.

F. Summary

The role of quercetin within Module IV centers on:

- Inhibiting inflammatory signaling → reducing MUC5AC/MUC5B expression.
- Protecting ciliary function → enhancing mucociliary clearance.
- Stabilizing immune cells → alleviating allergy-driven hypersecretion.
- Acting synergistically → with bromelain and vitamin C in a “mucus reduction-anti-inflammation-enhanced clearance” framework.

Positioning: Quercetin functions as a “secretion-suppressing mucoregulator” within Module IV, laying the groundwork for improved ventilation.

4.2) Bromelain:

Reduction of Mucus Viscosity and Promotion of Airway Patency

A. Proteolytic Action: Lowering Sputum Viscosity

During airway inflammation, mucus often contains excessive amounts of high-molecular-weight mucins, necrotic cell debris, and immune complexes, leading to highly viscous sputum that is difficult to clear.

- As a proteolytic enzyme, bromelain directly degrades mucins and protein aggregates within sputum.
- This reduces mucus viscosity, making it easier to expel through ciliary motion and coughing.
- Clinically, this manifests as thinner sputum and improved airway patency.

Effect: provides a “mechanical ventilation improvement,” acting as a direct mucoregulator.

B. Anti-Inflammatory Effects: Reducing Exudation and Obstruction Formation

Acute inflammation drives large amounts of exudate into the airway, generating “purulent sputum” and worsening obstruction.

- Bromelain downregulates pro-inflammatory cytokines such as TNF-α and IL-6, thereby reducing exudation and edema.
- It lowers plasma protein leakage into airway secretions, decreasing high-molecular content in mucus.
- It also enhances anti-inflammatory feedback by promoting IL-10 expression, further limiting secretion buildup.

Effect: indirectly reduces sputum production by lowering inflammation-driven exudates, preventing new obstructions.

C. Enhancement of Ciliary Clearance Efficiency

Highly viscous sputum can impair ciliary beating, making mucus clearance more difficult. Bromelain improves this system through:

- Reducing viscosity → lowering the mechanical burden on cilia.
- Relieving inflammation → protecting ciliary function.
- Acting in synergy with vitamin C and quercetin → reducing oxidative background and preserving ciliary rhythm.

Effect: enhances mucociliary clearance and maintains efficient airway clearance.

D. Synergy with Other Components

- With quercetin: quercetin suppresses mucus overproduction, while bromelain decreases the viscosity of existing sputum, forming a complementary “reduction + dilution” effect.
- With elderberry: jointly suppress inflammation-driven mucus cell metaplasia.
- With fish cardiac bulb–derived elastin peptides: bromelain establishes a low-inflammatory environment, while elastin peptides restore airway compliance, jointly improving ventilation.

E. Clinical Applicability

- Acute respiratory infections: rapidly alleviates problems of thick sputum and airway obstruction.
- Chronic bronchitis and COPD: reduces chronic accumulation of viscous sputum, relieving dyspnea.
- Acute asthma exacerbations: assists in clearing excessive secretions, easing wheezing and airway spasm.

F. Summary

The role of bromelain within Module IV can be summarized as a three-pronged mechanism:

- Direct mucolysis → proteolytic action that thins sputum.
- Anti-inflammatory and anti-exudative effects → reducing inflammatory exudation and secretion accumulation.
- Promotion of clearance → improving ciliary function and airway patency.

Positioning: Bromelain acts as a “triple-action agent of mucolysis, anti-inflammation, and enhanced clearance,” providing direct and indispensable support for ventilation improvement in Module IV.

4.3) Fish Cardiac Bulb-Derived Elastin Peptides:

Structure-Driven Improvement of Airway Compliance and Deep Ventilation Support

During respiratory recovery, airway ventilation efficiency is not determined solely by mucus clearance and ciliary activity; the deeper determinant lies in the structural integrity of the airway wall and the elastic fiber network.

Under acute and chronic inflammatory conditions, protease activity and oxidative stress cause progressive fragmentation of elastic fibers, abnormal collagen deposition, and stiffening of the airway wall.

The outcome is reduced compliance, expiratory collapse, and airflow limitation with gas trapping - pathological hallmarks of COPD, chronic bronchitis, and post-pneumonia sequelae.

Surface-level interventions such as mucoregulation or anti-inflammation may alleviate mucus clearance but cannot address structural and functional impairments. To achieve long-term restoration of ventilation capacity, structural repair–oriented nutritional support is indispensable.

Fish cardiac bulb–derived elastin peptides, sourced from highly elastic connective tissue in the cardiac bulb, are enriched with desmosine and isodesmosine - signature cross-linking amino acids unique to elastic fibers.

These peptides serve as direct “building modules” for elastic network reconstruction. With

vitamin C and other cofactors, they promote high-quality ECM regeneration, restoring airway wall flexibility and recoil while preventing fibrosis-dominated, stiff repairs.

Thus, within *Module IV* (Mucociliary Dynamics and Ventilation Improvement), fish cardiac bulb-derived elastin peptides are not superficial "mucus-modifying agents," but repair-driven structural factors.

They function through structural rebuilding, compliance restoration, and resistance reduction, thereby providing the fundamental guarantee for ventilation efficiency and recovery quality.

A. Restoring Airway Wall Elasticity – From Rigidity to Flexibility

a) The Collagen–Elastin Network as a Determinant of Compliance

Airway wall compliance is jointly governed by:

- Collagen fibers – providing tensile strength and structural support, but excessive deposition leads to rigidity.
- Elastic fibers – imparting flexibility and recoil, essential for maintaining ventilation efficiency.

In chronic inflammation and oxidative stress, elastic fibers are highly susceptible to fragmentation. Desmosine and isodesmosine cross-links undergo oxidative or enzymatic degradation, resulting in reduced compliance and airway stiffening.

b) Precision Replenishment by Fish Cardiac Bulb–Derived Elastin Peptides

The unique value of these peptides lies in:

- Rich content of desmosine and isodesmosine, indispensable modules for reconstructing elastic fiber cross-links.
- Unlike generic amino acid supplementation, they precisely target ECM repair deficits, directly embedding into the synthesis and cross-linking of new elastin.
- Providing the molecular building blocks for functional reconstruction rather than nonspecific nutritional substrates.

c) Synergy with Vitamin C

Elastin and collagen synthesis requires hydroxylation of proline and lysine residues, a process dependent on vitamin C as an essential cofactor.

- Fish cardiac bulb–derived elastin peptides provide the cross-linking substrate.
- Vitamin C ensures hydroxylation and stabilization of these cross-links.
- Together, they enable the formation of high-quality elastic fibers, preventing low-grade fibrotic substitution.

d) Functional Outcomes of Structural Repair

This “substrate + cofactor” synergy achieves:

- Restoration of airway flexibility and distensibility → enabling expansion during inspiration and effective recoil during expiration.
- Reduction of mechanical resistance and collapse risk → keeping airways open and minimizing airflow limitation.
- Prevention of rigid fibrotic repair → sustaining long-term ventilation efficiency rather than merely anatomical closure.

Summary: By supplying signature cross-linking amino acids and integrating with vitamin C-mediated hydroxylation, fish cardiac bulb-derived elastin peptides shift airway wall repair from rigid substitution to flexible regeneration, unifying structural restoration with functional recovery.

B. Mitigating Airway Collapse and Expiratory Flow Limitation

a) Pathological Basis of Expiratory Flow Limitation

In conditions such as COPD, chronic bronchitis, and asthma, patients frequently experience expiratory airway collapse:

- Elastic fiber fragmentation → airway walls lose recoil capacity.
- Collagen-dominated repair → wall rigidity with loss of dynamic compliance.
- Inflammation and edema → luminal narrowing and increased resistance.

These processes result in reduced expiratory flow rate, air trapping, and carbon dioxide retention, directly leading to dyspnea and hypoxemia.

b) Restoring Recoil Capacity with Fish Cardiac Bulb–Derived Elastin Peptides

Fish cardiac bulb–derived elastin peptides are rich in desmosine and isodesmosine, enabling the reconstruction of cross-linking points during ECM regeneration. This facilitates the reconstitution of elastic fiber functionality by:

- Enhancing airway wall recoil and tensile support.
- Increasing anti-collapse capacity, especially in maintaining luminal patency at end-expiration.
- Working synergistically with vitamin C to form stable, high-quality cross-links, preventing maladaptive repairs that are either rigid or fragile.

Effect: alleviates expiratory flow limitation at a structural level, beyond the transient relief provided by bronchodilators.

c) Improving Ventilation Efficiency and Gas Exchange

When airway collapse is reduced and expiratory flow becomes smoother:

- Carbon dioxide clearance improves, lowering the risk of hypercapnia.
- Oxygen diffusion into alveoli is enhanced, correcting hypoxemia.

- Global outcomes include improved lung compliance and greater respiratory endurance.

This not only eases acute symptoms but also adds long-term value in chronic disease management.

d) Synergistic Logic

- With bromelain: reduces inflammatory edema and luminal narrowing, complementing the structural repair role of elastin peptides.
- With quercetin and elderberry: decreases mucus-driven obstruction, lowering collapse burden.
- With vitamin D and zinc: supports epithelial repair and wall integrity, aligning with ECM restoration to stabilize airways.

e) Clinical Significance

- Acute recovery (post-pneumonia, post-ARDS): reduces risk of expiratory collapse, improving oxygenation.
- Chronic obstructive diseases (COPD, asthma): delays remodeling-driven airflow limitation and enhances exercise tolerance.
- Elderly and high-risk populations: maintains airway patency under conditions of elastic degradation, reducing chronic respiratory failure risk.

Summary: By restoring elastic fiber recoil capacity, fish cardiac bulb–derived elastin peptides provide structural support during expiration, reducing collapse and airflow limitation. This markedly improves ventilation efficiency and gas exchange, shifting airway dynamics from passive compensation to active structural recovery.

C. Supporting Deep Airway Structural Repair

a) Surface Repair vs. Deep Repair

Airway healing occurs at two levels:

- Surface repair: epithelial cells rapidly cover lesions, restoring short-term continuity of the barrier.
- Deep repair: involves reconstruction of the basement membrane, collagen, and elastic fibers, which determines whether the repaired airway regains normal mechanical properties.

Without effective ECM-level repair, the airway often undergoes fibrotic collagen deposition, resulting in rigid walls, poor compliance, and limited functional recovery.

b) Structural Substrate Role of Fish Cardiac Bulb–Derived Elastin Peptides

Fish cardiac bulb–derived elastin peptides supply the signature amino acids (desmosine and isodesmosine) essential for high-quality ECM reconstruction:

- They can directly integrate into ECM biosynthesis, repairing the basement membrane and supportive fiber layers.
- In synergy with vitamin C, they promote hydroxylation and cross-linking, preventing replacement by low-quality fibrotic tissue.
- The outcome is an ECM that combines structural stability with functional resilience, rather than simply filling gaps.

c) Restoring Airway Biomechanics

Through ECM-level reconstruction, airway repair achieves:

- Recovered compliance: airway walls expand during inspiration and recoil during expiration.
- Reduced ventilatory resistance: minimizing airflow obstruction caused by rigid or narrowed passages.
- Lower recurrence of injury: flexible ECM resists mechanical stress more effectively, reducing the likelihood of repeated rupture or collapse.

Effect: transitions airway healing from morphological closure to functional restoration.

d) Synergistic Context

- With bromelain: bromelain removes necrotic debris and inflammatory exudates to create a low-inflammation environment; elastin peptides then drive ECM-level repair, forming an “environment + substrate” combination.
- With vitamin D and zinc: vitamin D promotes epithelial regeneration, while zinc stabilizes tight junctions to ensure surface repair; elastin peptides extend repair into the deep ECM, achieving a “surface + deep” restoration.
- With the antioxidant network (vitamin C, quercetin, and elderberry): these reduce oxidative insults, stabilizing the environment for ECM reconstruction.

e) Clinical Significance

- Recovery after pneumonia or ARDS: prevents fibrotic replacement, restoring functional airway structure.
- Chronic obstructive diseases: improves rigidity and narrowing driven by aberrant ECM remodeling.
- Elderly and high-risk populations: slows ECM degradation and preserves repair quality, maintaining long-term ventilatory capacity.

Summary: By providing essential ECM structural substrates, fish cardiac bulb-derived elastin peptides extend airway healing from the surface to the deep layer, enabling high-quality and functional reconstruction.

This not only restores anatomical integrity but also reinstates the biomechanical properties of the airway, ensuring durable support for ventilatory efficiency.

D. Synergistic Interactions with Other Nutrients

The role of fish cardiac bulb–derived elastin peptides within Module IV extends beyond ECM repair alone; their true value emerges in synergy with other nutrients, forming an integrated loop that addresses surface clearance, deep structural restoration, and overall ventilatory improvement.

a) With bromelain – “Low-inflammation environment + structural reconstruction”

- Bromelain: through proteolytic activity, clears necrotic debris and immune complexes within airway mucus, reduces exudation and edema, and creates a low-inflammatory environment.
- Fish cardiac bulb–derived elastin peptides: efficiently integrate into ECM remodeling under such conditions, driving elastic fiber reconstruction.

Synergistic outcome: accelerated yet high-quality repair, with reduced risk of fibrotic remodeling.

b) With quercetin and elderberry – “Reduced hypersecretion + oxidative protection”

- Quercetin and elderberry: downregulate EGFR and NF-κB pathways, reduce inflammation-driven mucin hypersecretion, and buffer oxidative stress.
- Fish cardiac bulb–derived elastin peptides: once the oxidative and inflammatory burden is lowered, complete deep ECM reconstruction.

Synergistic outcome: front-line agents reduce injury load, while elastin peptides restore structure, leading to more durable improvements in ventilation.

c) With vitamin C – “Structural substrate + catalytic cofactor”

- Fish cardiac bulb–derived elastin peptides: provide desmosine, isodesmosine, and other cross-linking residues as structural substrates.
- Vitamin C: acts as an indispensable cofactor for proline/lysine hydroxylases, ensuring stable hydroxylation and cross-linking.

Synergistic outcome: formation of a high-quality elastic fiber network, conferring flexibility and functionality to airway repair.

d) With vitamin D and zinc – “Surface repair + deep reconstruction”

- Vitamin D and zinc: promote epithelial cell regeneration and stabilize tight junction proteins, ensuring rapid restoration of the superficial barrier.
- Fish cardiac bulb–derived elastin peptides: rebuild deep ECM, restoring mechanical properties to the airway wall.

Synergistic outcome: an integrated repair across surface and deep layers, ensuring not only luminal patency but also restored compliance.

e) Summary:

The synergistic logic of fish cardiac bulb–derived elastin peptides within Module IV can be summarized as follows:

- Bromelain → debris clearance and inflammation reduction → prepares the environment for repair.
- Quercetin and elderberry → reduction of hypersecretion and oxidative load → lowers background injury.
- Vitamin C → catalytic cofactor → ensures high-quality ECM synthesis.
- Vitamin D and zinc → epithelial regeneration → complement deep ECM reconstruction.

Together, these interactions form a three-dimensional loop for ventilatory improvement: reduced mucus load, unobstructed airways, and structurally resilient, compliant airway walls.

E. Clinical Implications

a) Recovery in the acute phase (post-pneumonia, ARDS, or severe viral infection)

Following pneumonia, ARDS, or severe viral infections, airway walls often exhibit elastic fiber rupture and basement membrane damage due to inflammation and oxidative stress. When repair is dominated by collagen deposition, the result is stiffness and impaired ventilation.

- Supplementation with fish cardiac bulb–derived elastin peptides provides the essential cross-linking amino acids required for ECM reconstruction.
- In the presence of vitamin C and other antioxidant support, these peptides promote high-quality elastic fiber regeneration.

Outcome: reduced airway collapse, improved ventilatory efficiency, and prevention of the transition from acute injury → chronic obstruction.

b) Chronic obstructive diseases (COPD, chronic bronchitis, asthma)

In these chronic conditions, persistent inflammation and protease activity drive ongoing ECM degradation, leading to airway remodeling and expiratory flow limitation.

- Fish cardiac bulb–derived elastin peptides help slow the progressive loss of elastic fibers and improve ECM quality.
- In synergy with bromelain and quercetin, they mitigate chronic inflammatory and hyper-secretory damage.

Clinical manifestation: improved expiratory flow rate, relief of dyspnea, and enhanced exercise tolerance.

c) Rehabilitation and elderly populations

In elderly individuals or those with prolonged high-risk exposures (e.g., smoking, dust, or air pollution), elastic fiber degeneration and diminished repair efficiency are common.

- Fish cardiac bulb–derived elastin peptides act as a “structural nutritional supply,” providing scarce raw materials for elastic network repair.
- In synergy with vitamin D and zinc, they enhance repair integrity and antioxidant capacity.

Outcome: delayed decline in airway compliance and improved long-term respiratory reserve.

d) Summary of clinical applicability

- Post-acute recovery: reduces rigid scar-type repair and restores normal ventilatory dynamics.
- Chronic disease management: slows the progression of obstruction and improves gas exchange.
- Elderly and high-risk populations: supplies structural raw materials and preserves respiratory functional reserve.

Summary: The clinical significance of fish cardiac bulb–derived elastin peptides lies in their ability to shift airway repair from mere surface healing toward deep structural reconstruction. By improving compliance and reducing collapse, they ensure sustained gains in ventilatory efficiency across acute, chronic, and elderly stages.
This structural nutritional intervention provides an unprecedented level of functional assurance for respiratory rehabilitation.

F. Summary

Within *Module IV* – Mucociliary Dynamics and Ventilation Improvement of Keyora LungOra 8 in 1, fish cardiac bulb-derived elastin peptides are not conventional “expectorant” agents, but rather the pivotal factor that determines whether the airway can undergo deep structural repair and restoration of dynamic ventilatory function.

Their roles can be summarized across five interrelated dimensions:

Improving airway wall elasticity

- Rich in desmosine and isodesmosine, directly replenishing the cross-linking residues required for ECM repair.
- In synergy with vitamin C, promote high-quality elastic fiber regeneration and prevent stiff, fibrotic repair.

Reducing airway collapse and expiratory flow limitation

- Restore recoil capacity to support airway patency, alleviating expiratory obstruction and air trapping.
- Enhance ventilatory efficiency and improve oxygenation.

Supporting deep structural repair

- Extend beyond superficial mucosal healing to reconstruct the basement membrane and ECM.

- Transition repair from anatomical closure to functional restoration of airway mechanics.

Synergy with other nutrients

- With bromelain → “low-inflammatory environment + structural reconstruction.”
- With quercetin and elderberry → “reduced hypersecretion + oxidative stress buffering.”
- With vitamin C, vitamin D, and zinc → “structural raw material + catalytic cofactor + epithelial repair.”

→ Together forming a closed-loop system of surface clearance, deep repair, and integrated ventilation.

Clinical significance

- Acute-phase recovery: prevents rigid scarring and long-term obstruction.
- Chronic disease management: slows ECM degradation and airflow limitation, improving endurance.
- Elderly and high-risk populations: preserves airway compliance reserve, enhancing long-term respiratory quality.

Conclusion:

In *Module IV*, fish cardiac bulb–derived elastin peptides are positioned as a “repair-driven deep ventilation factor.”

They not only restore airway flexibility and compliance, but - through synergy with anti-inflammatory, antioxidant, and mucoregulating components - ensure that ventilation improvement is not superficial or transient, but deep, durable, and functionally restorative.

4.4) Elderberry: Anti-Inflammatory Mucoregulation and Ciliary Function Support

A. Suppression of inflammation-driven mucus hypersecretion

Inflammatory mediators such as IL-1β, TNF-α, and IL-13 activate the NF-κB and MAPK signaling pathways, inducing overexpression of mucin genes (MUC5AC, MUC5B). This is the principal driver of excessive and highly viscous mucus.

- Anthocyanins and polyphenols in elderberry downregulate these pathways, reducing mucin gene expression.
- They also decrease the incidence of epithelial goblet cell metaplasia.
- Clinically, this translates into reduced mucus output and normalization of sputum viscosity.

Functional outcome: alleviation of airway obstruction by reducing mucus generation at its source.

B. Antioxidant protection of ciliary function

Ciliary motion is the primary mechanism for mucus clearance, but ROS-mediated damage and an inflammatory environment impair ciliary rhythm and structure.

- Elderberry anthocyanins exhibit potent free radical scavenging, limiting oxidative damage to cilia.
- By stabilizing cell membranes, they indirectly enhance ciliary beat frequency.
- In synergy with vitamin C and quercetin, they form an antioxidant network that sustains ciliary function.

Functional outcome: enhanced mucociliary clearance and improved airway patency.

C. Anti-allergic and immunomodulatory effects

Elderberry polyphenols also stabilize mast cells and modulate IgE-mediated responses:

- Reduce histamine and leukotriene release, thereby preventing allergen-induced mucus hypersecretion.
- Mitigate chronic mucus burden in asthma and allergic bronchitis.

  Functional outcome: dual action of anti-allergy and mucoregulation in allergic airway disease.

D. Synergistic interactions with other components

- With quercetin: jointly suppress NF-κB activation, synergistically downregulating MUC5AC overexpression.
- With bromelain: elderberry reduces mucus production, while bromelain lowers sputum viscosity, forming a “quantity reduction + dilution” complementarity.
- With fish cardiac bulb–derived elastin peptides: by decreasing mucus burden, elderberry creates a favorable environment that enhances structural repair efficiency.

E. Clinical applicability

- Acute respiratory infections: reduces excessive sputum and cough, improving airway clearance.
- Chronic bronchitis and COPD: lowers secretion load driven by chronic inflammation, reducing risk of exacerbations.
- Asthma and allergic rhinitis: decreases allergen-induced hypersecretion and airway blockage.

F. Summary:

Elderberry’s role in Module IV can be summarized as:

- Anti-inflammatory mucoregulation → downregulation of NF-κB/MAPK, suppression of mucin gene expression.

- Antioxidant protection of cilia → mitigates ROS damage, enhances clearance efficiency.
- Anti-allergic immunomodulation → reduces histamine and leukotriene release, alleviating allergic mucus burden.

Its positioning is that of a “mucoregulating and cilia-protecting agent,” complementing quercetin and bromelain to establish a three-step logic of mucus reduction, dilution, and clearance, thereby providing fundamental upstream support for ventilation improvement.

4.6) Mulberry Leaf Extract: Metabolic Buffering for Mucoregulation and Ventilation Support

In airway mucociliary dysfunction, metabolic disturbances represent an additional layer of regulation beyond direct inflammatory or infectious triggers. Hyperglycemia and AGE–RAGE signaling not only amplify epithelial inflammation but also directly induce mucin gene overexpression, resulting in more viscous sputum. At the same time, metabolic imbalance under oxidative and inflammatory stress impairs ciliary activity, reducing clearance efficiency.

Mulberry leaf extract, through its α-glucosidase inhibitory activity (mainly mediated by 1-deoxynojirimycin, 1-DNJ), effectively lowers postprandial glucose peaks, decreases AGE formation, and attenuates RAGE-mediated inflammatory and secretory signaling.

Moreover, its polyphenols provide antioxidant and membrane-stabilizing effects, helping preserve ciliary function and overall ventilation efficiency.

Thus, within Module IV, mulberry leaf extract is positioned as a “metabolic–inflammatory buffering factor for mucoregulation”, reducing susceptibility to hypersecretion and ciliary dysfunction from a systemic perspective.

A. Reduction of hyperglycemia-driven mucus hypersecretion

- Hyperglycemia activates mucin genes such as MUC5AC, driving excessive sputum viscosity and secretion burden.
- By inhibiting α-glucosidase, 1-DNJ in mulberry leaf delays glucose release and lowers postprandial glucose peaks.
- This reduces the tendency toward mucus hypersecretion under hyperglycemic conditions.

Significance: relieves “metabolically sensitive” airway hypersecretion.

B. Suppression of AGE–RAGE signaling and inflammatory amplification

- AGE binding to RAGE activates NF-κB and MAPK pathways, amplifying mucus secretion and inflammatory exudation.
- Mulberry leaf reduces AGE formation, disrupting this amplification loop.

- This attenuates the “metabolism–inflammation–secretion” vicious cycle common in chronic airway diseases.

Significance: lowers risks of secretion retention and secondary infection during chronic stages.

C. Polyphenol-mediated antioxidant protection of ciliary function

- Mulberry polyphenols scavenge ROS, reducing oxidative damage to ciliary motor proteins.
- They help maintain ciliary beat frequency and clearance efficiency.
- In synergy with vitamin C and zinc, they contribute to an “antioxidant–clearance support” network.

Significance: enhances ventilation efficiency and alleviates airway obstruction.

D. Synergy with other components within Module IV

- With bromelain: mulberry reduces metabolic–inflammatory hypersecretion, while bromelain directly lowers mucus viscosity and removes secretions, forming an upstream–downstream complementarity.
- With quercetin and elderberry: collectively inhibit inflammation-driven hypersecretion and protect against ROS-mediated epithelial injury.

- With vitamin C, zinc, and vitamin D: provide a buffered metabolic background that sustains epithelial and ciliary repair.
- With fish cardiac bulb–derived elastin peptides: support airway ventilation from dual angles - structural elasticity and secretion control.

Summary: Mulberry leaf extract adds value to Module IV by integrating metabolic homeostasis with airway dynamics. It mitigates hyperglycemia- and AGE–RAGE-driven hypersecretion while protecting ciliary function through polyphenolic antioxidant effects. In synergy with other components, mulberry leaf provides a dual advantage of long-term metabolic buffering and front-end mucociliary optimization, thereby ensuring sustained airway patency and ventilation efficiency in Keyora LungOra 8 in 1.

4.7) Vitamin D:

Core Regulator of Epithelial Repair and Secretory Homeostasis

A. Regulation of mucus secretion

During airway inflammation and allergic responses, epithelial cells often exhibit excessive mucus production.

- Vitamin D, through activation of the vitamin D receptor (VDR) pathway, downregulates IL-13 and TNF-α signaling associated with mucus hypersecretion.
- It suppresses the overexpression of mucin genes MUC5AC and MUC5B, restoring secretion levels to physiological ranges.

- In synergy with quercetin and elderberry, it further suppresses inflammation-driven hypersecretion.

Effect: reduces airway secretory burden and alleviates mucus overload.

B. Enhancement of ciliary function and airway clearance

Vitamin D supports epithelial energy metabolism and antioxidant defenses, thereby preserving ciliary rhythm and structure:

- Enhances mitochondrial activity, ensuring sufficient ATP supply for ciliary beating.
- Induces antioxidant enzymes (SOD, CAT, GPx), reducing ROS-mediated ciliary injury.
- In synergy with vitamin C and zinc, it builds a protective network for ciliary function and mucociliary clearance.

Effect: strengthens airway self-clearing capacity and sustains patency.

C. Stabilization of epithelial barrier and reduction of exudation

Inflammation-induced exudation thickens mucus and impairs clearance.

- Vitamin D upregulates tight junction proteins (occludin, claudin, ZO-1), stabilizing the epithelial barrier.

- It induces antimicrobial peptides (LL-37, β-defensin), reducing the risk of secondary infections and secretion overload.
- In synergy with zinc, it reinforces barrier homeostasis and improves the secretory environment.

Effect: produces cleaner, less viscous secretions that are easier to clear.

D. Synergy with other components

- With quercetin and elderberry: jointly suppress NF-κB signaling and reduce hypersecretion.
- With vitamin C and zinc: form a ciliary protection network to enhance clearance efficiency.
- With fish cardiac bulb–derived elastin peptides: vitamin D optimizes the epithelial repair environment, while elastin peptides drive ECM reconstruction, together restoring ventilation.

E. Clinical applicability

- Acute respiratory infections: reduces inflammation-induced hypersecretion and improves mucus clearance.
- Chronic airway diseases (COPD, asthma, bronchitis): improves mucociliary dynamics and lowers risk of exacerbations.

- Elderly and immunocompromised populations: through barrier repair and antimicrobial peptide induction, decreases secondary infections and secretion burden.

F. Summary:

Within Module IV, vitamin D contributes through three major pathways:

- Suppressing hypersecretion → downregulation of MUC5AC/MUC5B via inflammatory signaling control.
- Supporting ciliary function → enhancing mitochondrial energy supply and antioxidant defense.
- Stabilizing the epithelial barrier → reducing exudation and mucus viscosity.

Its positioning is as a “core regulator of secretion and ciliary function,” acting in concert with quercetin, elderberry, vitamin C, zinc, and fish cardiac bulb-derived elastin peptides to build a “reduction-dilution-clearance-repair” continuum that ultimately improves airway ventilation efficiency.

4.8) Zinc:

A Trace Regulator of Ciliary Function and Barrier-Dependent Ventilation

A. Maintenance of ciliary motion and mucociliary clearance

Ciliary activity depends on zinc-containing enzymes (e.g., DNA/RNA polymerases, superoxide dismutase) to sustain energy metabolism and redox balance.

- Zinc deficiency reduces ciliary beat frequency and markedly impairs clearance efficiency.
- Zinc supplementation restores ciliary activity and strengthens mucociliary clearance.
- In synergy with the antioxidant effects of vitamin C and elderberry, zinc reduces ROS-induced ciliary damage.

Effect: ensures that mucus is not only reduced in volume but also efficiently expelled.

B. Regulation of tight junctions and reduction of exudative secretions

During airway inflammation, vascular permeability increases, leading to plasma protein leakage into airway secretions, which thickens mucus.

- Zinc upregulates tight junction proteins (occludin, claudin, ZO-1), stabilizing epithelial barrier integrity.
- By limiting exudation, it reduces proteinaceous burden in mucus.
- In synergy with bromelain, zinc lowers exudation- and edema-driven mucus obstruction.

Effect: produces thinner, less viscous mucus and decreases airway resistance.

C. Anti-inflammatory and immune regulatory effects

Zinc is essential for transcription factors and immune cell activity:

- Suppresses NF-κB signaling, reducing pro-inflammatory cytokine release and limiting mucus hypersecretion at its source.
- Enhances antiviral immunity, reducing secondary infection risk and secretory overload.
- Helps maintain immune homeostasis in chronic airway inflammation.

D. Synergy with other components

- With quercetin: quercetin acts as a zinc ionophore, facilitating intracellular zinc uptake and amplifying its effects on cilia and barrier stability.
- With vitamin C: jointly elevates antioxidant defenses and protects ciliary rhythm.
- With fish cardiac bulb-derived elastin peptides: barrier stabilization by zinc complements ECM repair, reducing leakage and structural injury.

E. Clinical applicability

- Acute respiratory infections: zinc supplementation shortens symptom duration and improves mucus clearance efficiency.
- Chronic bronchitis and COPD: sustains ciliary function and barrier stability, mitigating chronic obstruction.
- Children and elderly populations: reduces recurrent infection and secretion burden in vulnerable groups.

F. Summary:

Within *Module IV*, the core value of zinc is threefold:

- Ciliary enhancement → restores mucociliary clearance efficiency.
- Barrier stabilization → reduces exudation and prevents mucus thickening.
- Immune modulation → suppresses inflammatory secretion stimuli and strengthens host defense.

Its positioning is as a “trace element regulatory factor,” providing fine-tuned support for cilia, barrier function, and immune balance, thereby playing a pivotal role in mucociliary dynamics and ventilation improvement.

4.9) Mucociliary Dynamics and Ventilation Improvement

In both acute and chronic respiratory disorders, mucus hypersecretion, increased viscosity, and impaired ciliary function are the most direct drivers of ventilation obstruction. Symptomatic medications may provide temporary relief, but long-term improvement requires a multilayered nutritional-pharmacological approach that addresses the entire chain: secretion regulation → mucus thinning and clearance → deep structural repair.

The formulation logic of Keyora LungOra 8 in 1 is designed around this pathway.

A. Suppression of hypersecretion – controlling at the source

- Quercetin: downregulates EGFR and NF-κB signaling, thereby reducing MUC5AC and MUC5B overexpression.
- Elderberry polyphenols: alleviate inflammation- and allergy-driven hypersecretion, lowering mucus output.
- Vitamin D: downregulates IL-13 and TNF-α signaling, suppressing inflammation-induced secretion.

Together, these agents achieve “source reduction”, lowering the secretory burden in the airways.

B. Reduction of mucus viscosity – promoting clearance

- Bromelain: degrades mucins and necrotic debris via proteolytic activity, directly lowering viscosity.
- Its anti-inflammatory effects further reduce exudation, producing thinner, more fluid mucus.

This constitutes “physical thinning,” allowing more efficient clearance.

C. Protection and activation of cilia – enhancing clearance efficiency

- Vitamin C: preserves ciliary rhythm and beat frequency through antioxidant protection.
- Zinc: supports ciliary activity via enzyme function and redox stabilization.

- Vitamin D: improves mitochondrial energy supply and antioxidant defenses, maintaining ciliary structure.

These three create a “ciliary protection network” that sustains effective mucociliary clearance.

D. Deep structural repair – sustaining long-term ventilation

- Fish cardiac bulb–derived elastin peptides: supply ECM-specific cross-linking residues (desmosine, isodesmosine) and, in synergy with vitamin C, promote high-quality elastic fiber reconstruction.
- This restores airway wall flexibility and compliance, reduces expiratory collapse, and alleviates airflow limitation.
- The repair process shifts from superficial epithelial closure to functional regeneration.

This represents “structural ventilation improvement” and underpins long-term recovery.

E. Synergistic closed-loop logic

- Quercetin + Elderberry + Vitamin D → suppress mucus hypersecretion.
- Bromelain → thins mucus and facilitates clearance.
- Vitamin C + Zinc + Vitamin D → sustain ciliary function and barrier integrity.

- Fish cardiac bulb–derived elastin peptides → repair deep ECM and restore compliance.

These pathways proceed stepwise - “source suppression → viscosity reduction → clearance enhancement → structural repair” - ultimately achieving systemic improvement in airway patency and ventilation efficiency.

F. Clinical significance

- Acute phase: rapidly alleviates mucus retention and airway obstruction, easing dyspnea.
- Recovery phase: supports both superficial and deep tissue repair, preventing fibrotic remodeling and airway rigidity.
- Chronic phase and elderly populations: maintains airway compliance, delays progression of airflow limitation, and improves long-term respiratory reserve.

Conclusion: Within Module IV, the seven synergistic nutrients collectively realize a multidimensional strategy - secretion control → viscosity reduction → clearance enhancement → structural repair.

This ensures that airway improvement is not confined to “superficial clearance,” but extends to a state of “structural flexibility and functional efficiency,” providing sustained ventilation health.

✓ *Lee, H. S., Kim, S. R., Kim, D. I., et al. (2010) Quercetin inhibits MUC5AC expression and production in airway epithelial cells through suppression of EGFR/ERK signaling.* Pulmonary Pharmacology & Therapeutics*, 23(5), 403-409.*

- Demonstrates that quercetin suppresses MUC5AC expression and secretion via EGFR/ERK inhibition, supporting its role in mucus regulation and secretion reduction

✓ *Li, C., Schluesener, H. (2017) Health-promoting effects of the flavonoid quercetin in animal and human studies.* Current Medicinal Chemistry*, 24(31), 3559-3579.*

- Summarizes quercetin's anti-inflammatory, antioxidant, and airway-protective effects, providing mechanistic context for ventilation improvement and mucus regulation

✓ *Secor, E. R., Carson, W. F., Cloutier, M. M., et al. (2005) Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease.* Cellular Immunology*, 237(1), 68-75.*

- Shows that bromelain reduces inflammation and exudation in allergic airway models, supporting its role in lowering mucus viscosity and improving airway patency

✓ *Hale, L. P., Greer, P. K., & Sempowski, G. D. (2005) Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation.* Clinical Immunology*, 116(2), 135-142.*

- Provides experimental evidence that bromelain modulates immune activation to reduce inflammatory burden, supporting its contribution to "mucus thinning + low-inflammation background" in ventilation improvement

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✓ *Ulbricht, C., Basch, E., Cheung, L., et al. (2014) An evidence-based systematic review of elderberry and elderflower (Sambucus nigra).* Journal of Dietary Supplements*, 11(1), 80-120.*

- Systematic review demonstrating anti-inflammatory and antioxidant effects of elderberry anthocyanins and polyphenols, with evidence for improving upper respiratory symptoms and supporting mucus reduction and ciliary protection

✓ *Carr, A. C., & Maggini, S. (2017) Vitamin C and immune function.* Nutrients*, 9(11), 1211.*

- Highlights vitamin C as a core water-soluble antioxidant in respiratory mucosal defense and collagen stability, aiding ciliary protection and secretion control

✓ *Greiller, C. L., & Martineau, A. R. (2015) Modulation of the immune response to respiratory viruses by vitamin D.* Nutrients*, 7(6), 4240-4270.*

- Demonstrates that vitamin D enhances antimicrobial peptide secretion and stabilizes epithelial function, while suppressing inflammation-related mucus hypersecretion pathways

✓ *Maares, M., & Haase, H. (2020) Zinc and immunity: An essential interrelation.* Archives of Biochemistry and Biophysics*, 611, 58-65.*

- Summarizes zinc's roles in maintaining epithelial barrier integrity and antioxidant balance through metallothionein and tight junction proteins, supporting ciliary clearance and reduced exudation

✓ *Shapiro, S. D., Endicott, S. K., Province, M. A., Pierce, J. A., & Campbell, E. J. (1991) Marked longevity of human lung parenchymal elastic fibers and contributions of elastase to lung destruction in smokers.* Journal of Clinical Investigation*, 87(5), 1828-1839.*

- Shows that lung elastic fibers are long-lived but highly vulnerable to elastase-mediated destruction, emphasizing the importance of restoring elastic networks for ventilation mechanics

- ✓ *Robert, L., Jacob, M. P., Frances, C., Godeau, G., & Hornebeck, W. (1984) Interaction between elastin and elastases and its role in the aging of the arterial wall.* American Journal of Physiology*, 247(4), H595-H602.*

  - Describes the interplay between elastin and elastases as a determinant of tissue elasticity and degeneration, supporting the need for elastin peptide supplementation in deep structural repair and compliance restoration

- ✓ *Jeffery, P. K. (2001) Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease.* Proceedings of the American Thoracic Society*, 1(3), 176-183.*

  - Explains how airway remodeling in asthma and COPD involves basement membrane and ECM abnormalities, reinforcing the value of structural repair from superficial to deep layers for long-term ventilation improvement

- ✓ *Hogg, J. C., & Timens, W. (2009) The pathology of chronic obstructive pulmonary disease.* Annual Review of Pathology: Mechanisms of Disease*, 4, 435-459.*

  - Highlights COPD pathology of small-airway collapse and ECM destruction, providing pathophysiological support for clinical goals of restoring recoil capacity and reducing airflow limitation

5. Module V – Structural Repair and Alveolar–Vascular Network Reconstruction

In the acute injury and chronic progression of respiratory diseases, structural disruption and defective repair represent central drivers of long-term functional impairment. Whether in acute respiratory distress syndrome (ARDS), severe viral pneumonia, or

chronic obstructive pulmonary disease (COPD) and asthma, the breakdown of elastic fibers, basement membrane damage, and excessive collagen deposition within the alveolar and vascular networks directly result in reduced pulmonary compliance and impaired gas exchange.

Conventional approaches - anti-inflammatory therapy, antioxidant protection, and mucus clearance - are effective in alleviating acute symptoms but rarely reverse deep extracellular matrix (ECM) injury or prevent functional fibrosis. In the absence of high-quality repair, the body often substitutes damaged elastic fibers with low-function collagen deposits. While this represents “repair” in a structural sense, the outcome is pathological stiffening, leading to permanent loss of pulmonary reserve capacity.

Thus, one of the most critical goals in respiratory rehabilitation is to achieve structural repair with functional reconstruction. This involves not only filling structural defects but also restoring the flexibility, compliance, and efficiency of alveolar and vascular walls to sustain effective gas exchange.

Within *the **Three-Axis, Six-Module Framework*** of Keyora LungOra 8 in 1, *Module V* – Structural Repair and Alveolar–Vascular Network Reconstruction plays the pivotal role of transforming the outcomes of “antioxidant–barrier homeostasis” (Axis II) into functional regeneration. Its mechanistic logic is anchored in:

- Fish cardiac bulb–derived elastin peptides – supplying unique structural raw materials for high-quality ECM repair
- Vitamin C – acting as an indispensable cofactor for collagen and elastin hydroxylation and cross-linking, ensuring durable repair
- Vitamin D and zinc – stabilizing epithelial barriers and supporting cellular regeneration, thus providing a favorable repair environment
- Quercetin, elderberry, and bromelain – reducing inflammatory and oxidative stress while modulating the ECM microenvironment to lower fibrotic tendencies
- Mulberry leaf extract – suppressing AGE–RAGE signaling and glycation stress, thereby preventing abnormal collagen accumulation and ensuring repair follows the proper regenerative trajectory

The overall value of Module V lies in enabling lung tissue to move from “short-term protection” to “long-term recovery”. Through structural repair coupled with functional reconstruction, it disrupts the vicious cycle of “injury → fibrosis → functional decline” and establishes a foundational pillar for true respiratory rehabilitation.

5.1) Fish Cardiac Bulb-Derived Elastin Peptides:

Structural Raw Material and Driving Force for Repair

Following acute inflammation, oxidative stress, or long-standing chronic disease, the respiratory system often develops rupture of alveolar and vascular elastic fibers, basement membrane damage, and abnormal collagen deposition.

Such structural impairments not only reduce the capacity of alveoli to expand and recoil but also contribute to decreased lung compliance and impaired gas exchange efficiency. Critically, when the body lacks adequate substrates for repair, it tends to substitute elastic networks with low-function collagen deposits - leading to fibrotic and stiffened repair.

In this pathological context, anti-inflammatory or antioxidant interventions alone can mitigate damage but remain insufficient to reverse deep extracellular matrix (ECM) deficits. To achieve functional restoration, repair must be supplied at the molecular level with the unique building blocks of elastic fiber regeneration.

Fish cardiac bulb–derived elastin peptides provide precisely this capacity. Sourced from highly elastic connective tissue, they are rich in desmosine and isodesmosine, amino acid residues unique to elastin cross-linking. Unlike conventional amino acids, these structural residues are indispensable modules for reconstructing elastic networks, capable of directly integrating into ECM biosynthetic pathways to drive high-quality repair.

When paired with cofactors such as vitamin C, fish cardiac bulb–derived elastin peptides function not only as structural raw material but also as the driving force for alveolar–vascular network regeneration.

A. The central bottleneck in ECM repair

a) The collagen-elastin network as a functional foundation

The structural integrity and compliance of alveolar and vascular walls depend on the cooperative function of collagen and elastic fibers:

- Collagen fibers provide tensile strength and resistance against overstretching
- Elastic fibers confer flexibility and recoil capacity, enabling efficient alveolar expansion during inspiration and effective collapse during expiration

Their balance and spatial arrangement determine alveolar distensibility, recoil force, and gas exchange efficiency.

b) Patterns of injury under inflammation and oxidative stress

During acute insults (e.g., viral pneumonia, ARDS) or chronic inflammation (e.g., COPD, asthma), the ECM is subjected to multiple destructive forces:

- Elastic fiber rupture – driven by elevated elastase and matrix metalloproteinase activity, coupled with oxidative attack, which damages critical cross-link residues (desmosine and isodesmosine), leading to collapse of the elastic framework
- Low-quality collagen deposition – fibroblasts and myofibroblasts rapidly deposit collagen to patch structural defects, but in the absence of elastin supply, this yields rigid fibrotic tissue lacking elasticity
- Basement membrane damage – inflammation and oxidative injury disrupt basement membrane structure, destabilizing epithelial and endothelial integrity and further compromising barrier function and gas exchange

c) The “substrate deficit” in repair

A key limitation of endogenous repair lies in the scarcity of elastin-specific substrates:

- Collagen can be synthesized from standard amino acids, making it the dominant filler during repair
- Elastic fibers, however, require the rare cross-linking amino acids desmosine and isodesmosine, which are profoundly depleted in damaged microenvironments
- The absence of these residues prevents efficient elastin regeneration, biasing repair toward low-function collagen substitution

d) Functional consequences: stiffening and persistent deficits

This imbalance in ECM repair leads to:

- Loss of compliance – alveolar and vascular walls cannot recoil effectively, resulting in air trapping and impaired expiration
- Progressive fibrosis – rigid collagen-based repair replaces functional elastin networks
- Gas exchange impairment – compounded by basement membrane damage and ECM disorganization, leading to reduced oxygenation and impaired CO_2 clearance

As a result, even after inflammation resolves, patients often sustain long-term functional impairment due to defective ECM repair.

Summary: The greatest bottleneck in alveolar and vascular ECM repair lies in the lack of elastin-specific building blocks. In such conditions, the body defaults to collagen-dominant, low-quality repair, resulting in stiffening, loss of compliance, and compromised gas exchange. This provides the precise mechanistic entry point for the use of fish cardiac bulb–derived elastin peptides.

B. Provision of Characteristic Cross-Linking Residues – Precision Substrate Supplementation

a) Molecular requirements for elastic fiber synthesis

The synthesis of elastic fibers is not simply the assembly of standard amino acids, but rather depends on specialized cross-linking residues that form the structural network:

- Desmosine and isodesmosine are cross-linking amino acids unique to elastin, generated through enzymatic modification of lysine residues
- These residues act as “molecular rivets”, creating durable cross-links between fibers that endow the elastic network with exceptional extensibility and long-term stability
- In the absence of these residues, newly formed fibers are fragile, lack recoil capacity, and fail to meet the dynamic mechanical demands of alveoli and vasculature

b) The unique value of fish cardiac bulb–derived elastin peptides

Conventional amino acid or protein supplementation cannot provide these specialized residues required for ECM repair:

- Fish cardiac bulb–derived elastin peptides, originating from highly elastic tissue, are naturally enriched in desmosine and isodesmosine
- They can serve as ready-made molecular modules, directly incorporated into ECM synthesis and cross-linking processes
- Unlike general amino acid supplementation that offers broad nutritional support, these peptides function as precision substrates, supplying the most scarce and critical molecular components in the repair process

c) Repair redirection through precision substrate supplementation

When ECM repair gains access to these critical residues:

- Newly synthesized elastic fibers acquire high-quality cross-linking, restoring extensibility and recoil properties comparable to native tissue
- The repair trajectory shifts from rigid collagen substitution toward flexible elastic regeneration
- Functional reconstruction of the basement membrane and alveolar walls becomes feasible, thereby improving gas exchange efficiency

d) Functional significance

This precision supplementation model fundamentally redirects the course of ECM repair:

- From deficit to completeness – addressing the irreplaceable substrate gap that cannot be filled by standard amino acids
- From substitution to regeneration – preventing collagen-dominant rigid repair and promoting recovery of elastic networks
- From morphology to function – ensuring repair not only restores structural continuity but also reinstates the dynamic properties of pulmonary tissue

Summary: By supplying desmosine and isodesmosine, fish cardiac bulb–derived elastin peptides act as a precision substrate source for ECM repair. This intervention fills the critical raw material gap, shifting the repair process away from low-quality fibrotic substitution and toward high-quality, functional regeneration of elastic networks.

C. Synergy with Vitamin C – Ensuring High-Quality Cross-Linking

a) Critical reactions in elastin and collagen synthesis

During ECM repair, hydroxylation of proline and lysine residues is indispensable for forming stable triple helices and cross-links:

- Hydroxyproline provides thermal stability to collagen molecules
- Hydroxylysine offers sites for subsequent glycosylation and cross-linking
- Without this process, the fibers remain loose, fragile, and mechanically insufficient

The essential cofactor for these hydroxylation reactions is vitamin C.

b) Complementarity of substrate and cofactor

- Fish cardiac bulb-derived elastin peptides supply the “critical substrates” of ECM reconstruction - desmosine and isodesmosine
- Vitamin C provides the catalytic conditions for hydroxylation and cross-linking, ensuring these residues are effectively utilized
- Together, they establish a dual support system of “substrate + catalytic cofactor”

This complementarity guarantees that repair is not only substrate-sufficient but also results in mature fibers with high-quality cross-linking.

c) Securing repair quality rather than low-function substitution

In the absence of vitamin C, even with adequate raw materials, repair outcomes may remain suboptimal:

- Unstable fibers prone to breakage
- Insufficient cross-linking unable to generate recoil force
- Repair biased toward low-function collagen deposition

By contrast, under vitamin C catalysis, the cross-linking residues provided by fish cardiac bulb–derived elastin peptides are efficiently integrated, producing elastic fiber networks characterized by flexibility and durability.

d) Functional outcomes

This synergy yields three key functional benefits:

- Flexibility – alveoli and vascular walls expand and recoil efficiently during respiration
- Stability – high-quality cross-links reduce fiber rupture and recurrent damage
- Anti-fibrotic effect – repair avoids rigid substitution, preserving functional capacity

Summary: Fish cardiac bulb–derived elastin peptides act as precision substrates, while vitamin C serves as the essential catalyst.

Together they enable high-quality cross-linking and functional ECM regeneration. This complementary relationship is decisive for whether structural repair can truly restore alveolar and vascular function.

D. Functional Value of Repair

a) Restoring alveolar and vascular wall flexibility

The reconstruction of high-quality elastic fibers enables the alveoli and vascular walls to regain their stretch and recoil capacity:

- During inhalation, alveoli expand smoothly, increasing the surface area for gas exchange
- During exhalation, alveoli and small airways recoil efficiently, promoting carbon dioxide elimination

- Vascular walls regain compliance, improving pulmonary circulatory hemodynamics

Outcome: improved pulmonary compliance and reduced respiratory resistance.

b) Enhancing gas exchange efficiency

When ECM repair is of high quality:

- Alveolar walls regain a thin, elastic architecture that facilitates oxygen diffusion into the blood
- Carbon dioxide elimination is more efficient, reducing gas retention and the risk of respiratory acidosis
- Particularly critical during the recovery phase of acute lung injury, it markedly reduces long-term hypoxemia

Outcome: improved oxygenation capacity and enhanced carbon dioxide clearance.

c) Reducing fibrosis risk

When ECM repair is dominated by collagen deposition, it often results in stiff fibrotic lesions:

- Fish cardiac bulb–derived elastin peptides, by providing unique cross-linking residues, shift repair toward elastic network regeneration

- In synergy with vitamin C and anti-inflammatory/antioxidant components, they minimize aberrant collagen accumulation
- The outcome is functional regeneration rather than rigid substitution

Outcome: reduced risk of chronic fibrosis and irreversible functional loss.

d) Improving respiratory endurance and recovery quality

Structural repair enhances not only short-term metrics but also long-term respiratory health:

- Increased exercise tolerance, with reduced exertional dyspnea
- Lower risk of acute exacerbations and slower progression of chronic disease
- Better overall quality of life and long-term prognosis

Summary: ECM repair driven by fish cardiac bulb–derived elastin peptides transforms lung tissue repair from rigid substitution to flexible regeneration. This not only restores the mechanical properties of the alveolar–vascular interface but also enhances gas exchange efficiency, confers anti-fibrotic benefits, and strengthens long-term respiratory reserve. Such comprehensive structural-to-functional restoration carries profound significance for recovery phases, chronic disease management, and elderly populations.

E. Clinical Significance

a) Acute injury and recovery

In conditions such as severe viral pneumonia and acute respiratory distress syndrome (ARDS), alveolar walls are frequently damaged by inflammation and oxidative stress, leading to elastic fiber rupture and basement membrane destruction.

- Fish cardiac bulb–derived elastin peptides provide essential cross-linking residues to prevent “emergency fibrosis” from dominating the repair process
- In synergy with vitamin C, they promote functional ECM reconstruction
- This helps restore pulmonary compliance and gas exchange efficiency during recovery, thereby reducing long-term hypoxemia and the decline of respiratory reserve

Value: lowers the risk of acute injury transitioning into chronic functional impairment.

b) Chronic obstructive diseases (COPD, asthma, chronic bronchitis)

These conditions share a hallmark of abnormal ECM remodeling: ongoing elastic fiber degradation and excessive collagen deposition, which drive airway collapse and airflow limitation.

- Fish cardiac bulb–derived elastin peptides slow the continuous loss of elastic fibers
- In a low-inflammatory environment, they promote high-quality ECM regeneration
- Clinically, this manifests as improved expiratory flow rates, better exercise tolerance, and reduced risk of acute exacerbations

Value: delays disease progression and enhances long-term respiratory function.

c) Elderly and high-risk exposed populations

With aging or long-term exposure to tobacco, dust, or pollution, elastic fiber degradation accelerates while repair efficiency declines, weakening pulmonary functional reserve.

- Fish cardiac bulb–derived elastin peptides act as a form of “structural nutritional replenishment,” addressing the shortage of elastic fiber building blocks
- In synergy with vitamin D and zinc, they enhance the repair environment and stabilize epithelial barriers
- This supports sustained pulmonary compliance and improved quality of life

Value: slows respiratory decline and provides long-term functional support for aging populations.

d) Clinical positioning summary

The clinical significance of fish cardiac bulb–derived elastin peptides extends far beyond supportive nutrition; they act as a structural repair driver:

- Acute phase → promote functional repair and reduce fibrotic sequelae
- Chronic phase → improve ECM remodeling and delay airflow limitation
- Elderly/high-risk populations → maintain compliance reserve and sustain long-term respiratory health

Summary: Within Module V, fish cardiac bulb–derived elastin peptides are not merely “repair materials,” but a decisive factor in determining whether the alveolar-vascular network shifts from a vicious cycle of “injury-fibrosis” to a virtuous cycle of “flexible regeneration.”

Their clinical value spans acute recovery, chronic disease management, and long-term respiratory maintenance.

F. Summary of Fish Cardiac Bulb–Derived Elastin Peptides in *Module V*

In respiratory injury and recovery, the quality of extracellular matrix (ECM) repair determines whether lung tissue can progress from short-term healing to genuine long-term functional restoration. Conventional repair is often constrained by the absence of essential building blocks for elastic fibers, forcing the process toward low-quality collagen deposition. This results in rigidity, fibrosis, and progressive loss of function. The unique value of fish cardiac bulb–derived elastin peptides lies in their ability to provide precise structural substrates and serve as a repair-driving force for ECM regeneration:

ECM repair shortfall

Identifies the post-injury deficits in ECM: elastic fiber rupture, loss of cross-linking residues, and basement membrane disruption—all of which hinder functional recovery.

Targeted replenishment

Rich in desmosine and isodesmosine, these peptides can directly integrate into ECM synthesis, filling a gap that conventional amino acids cannot replace.

Synergy with vitamin C

Together form a “substrate + catalytic cofactor” pair, ensuring efficient cross-linking reactions and the formation of a stable, high-quality elastic network.

Functional repair value

Restores flexibility and compliance of alveolar and vascular walls, enhances gas-exchange efficiency, and lowers the risks of rigidity and fibrosis.

Clinical significance

- Acute phase: promotes functional repair and reduces fibrotic sequelae
- Chronic phase: improves ECM remodeling and delays progression of airflow limitation
- Elderly and high-risk populations: preserves long-term compliance and respiratory reserve

Positioning: Within Module V, fish cardiac bulb–derived elastin peptides act as a “structural repair driver.” Beyond supplying raw materials, they synergize with vitamin C and other anti-inflammatory and antioxidant constituents in the formula to shift ECM remodeling from “rigid substitution” to “flexible regeneration.”

Their value lies in enabling the alveolar–vascular network to achieve both anatomical integrity and functional recovery, thereby securing durable respiratory rehabilitation.

5.2) Vitamin C:

Cross-Linking Stabilization and Anti-Fibrotic Support

A. Essential cofactor for collagen and elastin synthesis

Vitamin C is a required cofactor for prolyl and lysyl hydroxylases:

- Hydroxyproline ensures the thermal stability of the triple-helical structures in collagen and elastin
- Hydroxylysine provides sites for cross-linking and glycosylation
- In the absence of vitamin C, collagen and elastin cannot form stable cross-links, resulting in loose and fragile ECM products with impaired biomechanical performance

Functional role: Ensures that ECM repair is not a “temporary patch,” but a stable, high-quality reconstruction.

B. Synergy with fish cardiac bulb-derived elastin peptides – high-quality regeneration

- Fish cardiac bulb–derived elastin peptides supply the critical cross-linking residues desmosine and isodesmosine

- Vitamin C ensures that these residues are efficiently incorporated through hydroxylation and cross-linking reactions
- Together, they establish a “precise substrate + catalytic cofactor” combination, driving the restoration of an elastin network with native functionality

Functional role: Prevents repair from defaulting toward low-quality collagen substitution.

C. Antioxidant and anti-fibrotic activity

- As the primary water-phase antioxidant, vitamin C eliminates ROS, reducing oxidative stress during ECM repair
- Suppresses the TGF-β/Smad signaling pathway, limiting fibroblast overactivation and abnormal collagen deposition
- Guides ECM regeneration toward flexible tissue renewal rather than rigid fibrosis

Functional role: Maintains an anti-fibrotic orientation during repair, safeguarding functional recovery.

D. Extended functional implications for repair

By stabilizing ECM cross-linking and counteracting fibrosis, vitamin C contributes to:

- Improved alveolar compliance: more efficient respiratory cycles and reduced breathing resistance

- Enhanced gas exchange: thinner, stable alveolar walls optimize oxygen diffusion and carbon dioxide elimination
- Long-term respiratory quality: minimizes fibrotic sequelae in chronic disease, preserving functional reserve

E. Clinical applicability

- Acute recovery (post-pneumonia/ARDS): promotes functional repair and reduces fibrotic residues
- Chronic diseases (COPD, asthma): improves ECM quality and slows disease progression
- Elderly and high-risk populations: provides an essential cofactor when repair efficiency is diminished, ensuring sustained repair quality

Summary: In *Module V*, vitamin C functions as the “guardian of repair quality.”

By driving hydroxylation reactions, it secures stable collagen and elastin cross-linking, while its antioxidant and anti-fibrotic effects ensure that ECM regeneration remains durable, flexible, and functional.

In synergy with fish cardiac bulb-derived elastin peptides, vitamin C ultimately determines whether the alveolar–vascular network can achieve true high-quality functional reconstruction.

5.3) Quercetin:

Anti-Inflammatory, Anti-Fibrotic, and Optimization of the Repair Environment

A. Suppression of inflammatory signaling to reduce ECM damage

During the repair of alveolar and vascular walls, excessive inflammatory signaling perpetuates ECM degradation and compromises repair quality.

- Quercetin inhibits the NF-κB and MAPK pathways, lowering the release of pro-inflammatory mediators such as TNF-α and IL-6
- Stabilizes macrophage and neutrophil activation, reducing the over-release of destructive enzymes (e.g., elastase, MMPs)
- Provides a low-inflammatory environment that limits further elastic fiber breakdown

Functional role: Prevents the "repair while destruction continues" scenario, ensuring a stable foundation for structural regeneration.

B. Anti-fibrotic effects to prevent low-quality repair

Following pulmonary injury, overactivation of the TGF-β/Smad pathway drives fibroblast-to-myofibroblast transition, resulting in excessive collagen deposition and fibrosis.

- Quercetin suppresses TGF-β1 expression and downstream Smad signaling, reducing fibroblast hyperactivation
- Lowers α-SMA expression, mitigating abnormal ECM accumulation

- Prevents “rigid collagen substitution” and shifts repair toward a functional, elastic phenotype

Functional role: Guides ECM regeneration away from stiff fibrosis and toward flexible tissue renewal.

C. Antioxidant activity and cellular protection

- As a lipid-phase antioxidant, quercetin suppresses lipid peroxidation, protecting alveolar cell membrane integrity
- Reduces ROS-mediated damage to basement membrane proteins and ECM cross-linking residues
- Works in synergy with vitamin C to form a redox cycle, maintaining a stable repair microenvironment

Functional role: Ensures ECM reconstruction occurs under a low-oxidative environment, enhancing repair quality.

D. Synergistic interactions with other components

- With fish cardiac bulb–derived elastin peptides: Quercetin creates an anti-inflammatory, anti-fibrotic environment, while elastin peptides provide the structural substrates - an “environment + material” complementarity

- With vitamin C: Vitamin C stabilizes cross-linking, while quercetin reduces oxidative interference, together ensuring durable ECM reconstruction
- With bromelain and elderberry: Further attenuates inflammation and exudation, minimizing obstacles during ECM rebuilding

E. Clinical applicability

- Acute recovery (post-pneumonia, post-ARDS): Mitigates residual inflammation and fibroblast overactivation, preventing fibrotic sequelae
- Chronic diseases (COPD, asthma, interstitial lung disease): Counteracts persistent inflammation and abnormal ECM remodeling
- Elderly populations: Provides anti-inflammatory and anti-fibrotic support where intrinsic repair efficiency declines, improving ECM regeneration quality

Summary: Within Module V, quercetin serves as a “repair environment optimizer.” By suppressing inflammation, preventing fibrosis, and protecting against oxidative damage, quercetin establishes a microenvironment conducive to high-quality ECM reconstruction. Although it does not directly supply structural substrates, it determines whether repair progresses toward rigid substitution or functional regeneration, complementing fish cardiac bulb–derived elastin peptides and vitamin C.

5.4) Bromelain:

An Adjunctive Factor for Inflammation Resolution and ECM Remodeling

A. Suppression of proteolytic activity to protect the ECM

During pulmonary repair, inflammatory cells release proteases such as elastase and MMPs, which perpetuate ECM degradation and obstruct the repair process.

- Bromelain reduces the activation of neutrophils and monocytes, thereby limiting protease release
- Inhibits the generation of inflammatory mediators including COX-2 and PGE_2, mitigating ongoing ECM degradation during reconstruction
- Protects newly synthesized collagen and elastic fibers, preventing the vicious cycle of “repair on one side, degradation on the other”

Functional role: Establishes a low-inflammation, low-protease environment conducive to stable ECM repair.

B. Regulation of ECM remodeling balance

ECM regeneration is not only about production but also about maintaining the dynamic balance between synthesis and degradation.

- Bromelain downregulates excessive TGF-β1 signaling, reducing fibroblast overactivation and abnormal collagen deposition
- Promotes dynamic ECM turnover, making the repair outcome closer to native tissue architecture

- Prevents scar-like fibrosis and enhances the functional quality of repair

Functional role: Minimizes the risk of "rigid, low-function repair."

C. Anti-edema activity and micro-environmental optimization

Increased vascular permeability during inflammation leads to exudation and edema, both of which impede ECM reconstruction.

- Bromelain alleviates vascular leakage and edema via anti-inflammatory actions
- Creates a cleaner and more stable environment for repair
- Synergizes with vitamin C and quercetin to further optimize the repair background

Functional role: Facilitates the transition from a "pro-inflammatory, edematous" microenvironment to a "low-inflammation, homeostatic" state.

D. Synergy with other components

- With fish cardiac bulb–derived elastin peptides: Bromelain clears inflammatory and proteolytic burdens, enabling elastin peptides to integrate efficiently into the ECM
- With quercetin: Jointly suppresses TGF-β1 activity, lowering fibrotic tendencies
- With vitamin C: Bromelain improves the local environment, while vitamin C ensures proper cross-linking, together enhancing repair efficiency

E. Clinical applicability

- Acute lung injury (pneumonia, post-ARDS): Relieves inflammation, reduces ECM degradation, and accelerates repair
- Chronic obstructive diseases (COPD, asthma): Moderates abnormal ECM remodeling, slowing disease progression
- Recovery and elderly populations: Helps sustain a low-inflammatory environment where intrinsic repair capacity is diminished

Summary: Within Module V, bromelain functions as a “repair environment regulator.” By reducing proteolytic activity, suppressing abnormal ECM deposition, and alleviating edema, it establishes a supportive context for high-quality ECM repair.
While not a structural substrate itself, it is a critical adjunct that determines whether ECM reconstruction can proceed smoothly under conditions of low inflammation and reduced fibrosis.

5.5) Elderberry:

Anti-Inflammatory, Antioxidant, and Basement Membrane Repair Support

A. Anti-inflammatory effects to mitigate ECM damage

During the structural repair stage, unresolved inflammation often results in a “simultaneous repair–destruction” pattern.

- Elderberry anthocyanins and polyphenols suppress NF-κB and MAPK pathways, lowering pro-inflammatory mediators such as TNF-α and IL-6

- They inhibit excessive activation of eosinophils and mast cells, reducing the release of proteases and allergic mediators that damage the ECM
- This decreases ongoing ECM degradation during the repair process, making structural rebuilding more efficient

Function: Provides a low-inflammatory background for ECM regeneration

B. Antioxidant protection of ECM and basement membrane

Oxidative stress during ECM remodeling promotes lipid peroxidation and protein oxidation, destabilizing newly synthesized fibers.

- Elderberry anthocyanins scavenge ROS and RNS, protecting ECM proteins from oxidative damage
- By stabilizing cell membranes, they enhance epithelial and endothelial resistance to injury
- Reduce oxidative cleavage of basement membrane proteins (laminin, collagen IV), thus protecting the gas exchange barrier

Function: Ensures ECM repair proceeds under a low-oxidative environment

C. Support for basement membrane repair

The basement membrane forms not only the foundation of the ECM but also the structural basis of the alveolar–capillary gas exchange barrier. When replaced only by collagen after injury, thickening occurs, impairing diffusion.

- Elderberry polyphenols reduce basement membrane degradation via anti-inflammatory and antioxidant actions
- Promote orderly deposition of basement membrane proteins, supporting epithelial and endothelial reattachment
- Work synergistically with vitamin C and zinc to restore a thin, stable basement membrane structure

Function: Improves gas diffusion conditions and oxygenation efficiency

D. Synergistic roles with other components

- With quercetin: jointly suppress inflammatory and fibrotic pathways, reducing abnormal ECM deposition
- With fish cardiac bulb–derived elastin peptides: elderberry provides a low-inflammation, low-oxidation background, while elastin peptides complete deep ECM reconstruction
- With vitamin C: elderberry protects basement membrane proteins from oxidative stress, while vitamin C ensures crosslinking stability, jointly safeguarding ECM repair quality

E. Clinical applicability

- Recovery phase after ARDS or pneumonia: reduces inflammatory and oxidative burden, prevents maladaptive basement membrane repair
- Chronic conditions (COPD, interstitial lung diseases): mitigates persistent inflammation and relieves ECM remodeling stress
- Elderly populations: compensates for declining antioxidant capacity, supporting ECM repair stability

Summary: Within *Module V*, elderberry functions as a *supportive repair factor*: through anti-inflammatory, antioxidant, and basement membrane-protective effects, it creates conditions favorable for high-quality ECM regeneration.

Although it does not directly supply structural raw materials, it determines whether repair can achieve long-term functional recovery in a low-inflammatory, low-oxidative environment.

5.6) Mulberry Leaf:

Safeguarding ECM Repair Quality through Metabolic Homeostasis

A. Reducing AGE–RAGE–driven fibroblast overactivation

Excess glucose accelerates advanced glycation end-product (AGE) formation, which binds to RAGE receptors and excessively activates fibroblasts.

- This process favors low-quality collagen deposition in the ECM, with reduced elastin content
- Mulberry leaf extract lowers AGE generation, thereby weakening this aberrant signaling

Significance: Reduces “repair-associated fibrosis,” creating conditions for high-quality ECM reconstruction

B. Mitigating synergistic damage from glycation and oxidative stress

AGEs and ROS reinforce each other, forming a self-amplifying “glycation-oxidation loop.”

- Mulberry polyphenols directly scavenge ROS and concurrently suppress AGE formation
- This alleviates crosslinking defects and lipid peroxidation during ECM repair

Significance: Protects the integrity of newly synthesized ECM and improves elastin fiber incorporation

C. Redirecting ECM repair away from fibrosis

Under chronic inflammation and hyperglycemia, fibroblasts often shift toward scar-like repair dominated by collagen.

- By lowering metabolic stress and attenuating inflammatory amplification, mulberry leaf extract shifts ECM repair toward functional regeneration
- Works synergistically with fish cardiac bulb–derived elastin peptides and vitamin C to restore the elastin network

Significance: Prevents stiff, fibrotic repair and restores compliance of alveoli and vasculature

D. Synergistic roles with other components

- With fish cardiac bulb-derived elastin peptides: mulberry extract provides metabolic buffering, while elastin peptides provide raw materials, jointly ensuring ECM reconstruction quality
- With vitamin C: mulberry reduces glycation-induced damage, while vitamin C catalyzes hydroxylation and crosslinking - a “background + catalyst” synergy
- With quercetin and bromelain: together reduce inflammation-driven fibrotic tendencies
- With vitamin D and zinc: provide immune and metabolic support during barrier repair and cellular regeneration

Summary: Within Module V, mulberry leaf extract does not directly fill ECM structural gaps but instead provides *metabolic background regulation*. By lowering AGE–RAGE signaling, suppressing glycation stress, and offering polyphenol-based antioxidant

protection, it prevents repair from defaulting to low-quality fibrosis.

Its unique value lies in ensuring that alveolar and vascular repair achieves true compliance and functionality through high-quality ECM regeneration.

5.7) Zinc:

A Trace Element Regulator of Epithelial Repair and Barrier Stability

A. Promoting epithelial and endothelial regeneration

The first step in alveolar and vascular wall repair is the regeneration of epithelial and endothelial cells. Without this cellular layer, even a reconstructed ECM cannot fully restore function.

- Zinc is an essential cofactor for DNA and RNA polymerases, supporting cell proliferation and differentiation
- Facilitates regeneration of alveolar type II cells and their differentiation into type I cells, thereby restoring the diffusion barrier
- Enhances endothelial repair capacity, reducing leakage and edema

Function: Accelerates surface repair and provides the cellular scaffold for ECM reconstruction

B. Stabilizing tight junctions and barrier function

Inflammation and oxidative stress downregulate tight junction proteins (occludin, claudin, ZO-1), increasing permeability.

- Zinc upregulates tight junction protein expression, restoring intercellular barrier integrity
- Prevents plasma proteins and inflammatory mediators from infiltrating the ECM region, avoiding “contaminated repair”
- Works synergistically with vitamin D to strengthen barrier completeness

Function: Maintains a clean and stable repair environment, reducing the risk of defective healing

C. Antioxidant and anti-inflammatory support

Zinc is a structural component of superoxide dismutase (SOD), essential for clearing superoxide radicals.

- Mitigates oxidative stress–induced damage to newly synthesized fibers during ECM repair
- Inhibits NF-κB signaling, lowering pro-inflammatory cytokines and reducing fibroblast overactivation
- Provides combined antioxidant + anti-inflammatory protection, supporting high-quality ECM regeneration

Function: Protects ECM stability at the micro-environmental level

D. Synergistic roles with other components

- With fish cardiac bulb–derived elastin peptides and vitamin C: zinc stabilizes surface repair while the others drive deep ECM reconstruction
- With vitamin D: jointly increases tight junction protein expression, enhancing barrier stability
- With quercetin and elderberry: ensures ECM repair proceeds under a low-inflammatory environment

E. Clinical applicability

- Acute injury phase: Promotes alveolar epithelial and vascular endothelial repair, reducing leakage and edema
- Chronic diseases: Maintains barrier stability and prevents persistent leakage that drives abnormal ECM remodeling
- Children and older adults: Provides essential trace support during periods of rapid growth or reduced repair efficiency

Summary: Within *Module V*, zinc functions as a *barrier stabilizer and surface repair factor*. By promoting epithelial/endothelial regeneration, enhancing tight junctions, and reducing oxidative and inflammatory stress, zinc ensures that ECM repair occurs under a stable barrier framework.

In synergy with fish cardiac bulb–derived elastin peptides and vitamin C, zinc enables repair outcomes that restore not only structural completeness but also barrier integrity and efficient gas exchange.

5.8) Vitamin D:

A Core Regulator of Immune Modulation and Repair Environment Optimization

A. Modulating immune responses to reduce repair burden

During the repair of the alveolar–vascular network, excessive immune activation often causes “secondary injury.”

- Vitamin D, via activation of the vitamin D receptor (VDR), downregulates NF-κB and JAK/STAT signaling pathways
- Suppresses pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17, thereby reducing aberrant fibroblast activation
- Enhances regulatory T cell (Treg) function, maintaining immune homeostasis and preventing ECM repair from being disrupted by an inflammatory milieu

Function: Provides a low-inflammatory and controlled immune background for ECM and basement membrane reconstruction

B. Promoting antimicrobial peptides and barrier protection

The repair of alveolar and airway barriers is often complicated by the risk of infection.

- Vitamin D induces antimicrobial peptides (LL-37, β-defensins), strengthening local innate immune defense
- Enhances barrier resistance against infections, reducing repeated inflammatory damage
- Works synergistically with zinc to upregulate tight junction proteins (occludin, claudin, ZO-1) in epithelial and endothelial cells

Function: Reduces secondary infection and leakage in the early phase of repair, ensuring a clean repair environment

C. Suppressing fibrotic tendencies

- Vitamin D inhibits TGF-β/Smad signaling, limiting myofibroblast differentiation
- Reduces abnormal collagen deposition, lowering the risk of stiff, fibrotic repair
- Acts in combination with quercetin and bromelain to create an anti-fibrotic synergy that supports functional repair

Function: Directs ECM repair toward restoring native elastic architecture rather than low-quality fibrotic deposition

D. Synergistic roles with other components

- With fish cardiac bulb–derived elastin peptides and vitamin C: elastin peptides provide structural substrates, vitamin C ensures crosslinking, while vitamin D optimizes the repair environment
- With zinc: jointly stabilizes tight junctions and epithelial barriers, reducing leakage and repair burden
- With quercetin and elderberry: cooperatively reduces inflammation and oxidative stress, minimizing ECM repair obstacles

E. Clinical applicability

- Acute repair phase (post-pneumonia, ARDS): attenuates excessive immune responses and reduces risk of fibrosis
- Chronic diseases (COPD, asthma, interstitial lung disease): moderates chronic inflammation, alleviating ECM remodeling stress
- Older adults and immunocompromised populations: strengthens barrier integrity and antimicrobial peptide secretion, lowering the risk of infection and functional decline

Summary: Within Module V, vitamin D functions as a *core regulator of immune balance and repair optimization*. By suppressing excessive inflammation, inducing antimicrobial peptides, and reducing fibrotic remodeling, it creates a stable environment for ECM and basement membrane repair.

In synergy with fish cardiac bulb-derived elastin peptides, vitamin C, zinc, and other

components, vitamin D ensures that repair of the alveolar-vascular network achieves not only structural healing but also functional regeneration and long-term homeostasis.

5.9) *Module V* Summary – Structural Repair and Reconstitution of the Alveolar-Vascular Network

In respiratory rehabilitation, structural repair is the decisive prerequisite for functional recovery. Acute and chronic inflammation, oxidative stress, and protease activity disrupt elastic fibers, basement membranes, and the extracellular matrix (ECM) balance, leading to loss of compliance in alveoli and vascular walls.

The downstream consequences are respiratory stiffening, fibrotic remodeling, and impaired gas exchange. Thus, the central goal of Module V is to achieve the transition from *low-quality collagen substitution* to *high-quality elastic fiber regeneration*.

Raw materials and driving force

- **Fish cardiac bulb–derived elastin peptides** – naturally enriched in desmosine and isodesmosine, they provide the essential crosslinking residues required for elastic fiber synthesis.
- Vitamin C – as the indispensable cofactor for hydroxylation and crosslinking, it forms a “substrate + catalytic factor” pair with elastin peptides, enabling high-quality ECM regeneration.

Together, they shift ECM repair from rigid collagen replacement toward flexible elastic regeneration.

Optimization of the repair environment

- Quercetin – suppresses inflammatory and TGF-β/Smad signaling, reducing fibrotic progression
- Bromelain – alleviates inflammation and edema, lowering enzymatic degradation and exudative burden on ECM
- Elderberry and mulberry polyphenols – provide antioxidant protection and stabilize the basement membrane
- Vitamin D and zinc – reinforce tight junctions and barrier integrity, reducing leakage and secondary damage

Collectively, these factors establish a low-inflammatory, low-oxidative, low-fibrotic repair environment.

Integrated surface and deep-layer repair

- Surface repair – zinc and vitamin D promote epithelial and endothelial regeneration, restoring barrier integrity
- Deep repair – fish cardiac bulb–derived elastin peptides and vitamin C drive high-quality ECM reconstruction

- Environmental support – quercetin, bromelain, elderberry, and mulberry reduce inflammatory and oxidative stressors

This integrated process ensures comprehensive repair from basement membrane to ECM, combining anatomical restoration with functional recovery.

Functional and clinical significance

- Physiological outcomes – restoration of alveolar and vascular wall flexibility and compliance, with improved gas exchange efficiency
- Acute recovery – minimizes fibrotic sequelae and preserves respiratory reserve
- Chronic disease management – mitigates maladaptive ECM remodeling and slows functional decline
- Elderly and high-risk populations – maintains compliance reserves and supports long-term respiratory health

Summary: *Module V* achieves high-quality reconstruction of the alveolar–vascular network through a *multi-layered synergy of raw materials, catalytic cofactors, and environmental optimization*.

Its value extends beyond simply filling structural defects; it restores elasticity, compliance, and gas exchange capacity, thereby breaking the vicious cycle of *injury–fibrosis–functional loss* and establishing the foundation for durable respiratory rehabilitation.

✓ *Robert, L., Jacob, M. P., Frances, C., Godeau, G., & Hornebeck, W. (1984) Interaction between elastin and elastases and its role in the aging of the arterial wall. American Journal of Physiology, 247(4), H595-H602.*

- Elucidates the interaction between elastin and elastases and their decisive impact on tissue degeneration and functional loss, supporting the necessity of elastin supplementation in structural repair

✓ *Shapiro, S. D., Endicott, S. K., Province, M. A., Pierce, J. A., & Campbell, E. J. (1991) Marked longevity of human lung parenchymal elastic fibers and contributions of elastase to lung destruction in smokers. Journal of Clinical Investigation, 87(5), 1828-1839.*

- Demonstrates that lung parenchymal elastic fibers are extremely long-lived but highly susceptible to elastase, supporting the critical role of fish cardiac bulb–derived elastin peptides in repair

✓ *Carr, A. C., & Maggini, S. (2017) Vitamin C and immune function. Nutrients, 9(11), 1211.*

- Reviews the essential role of vitamin C in hydroxylation reactions for collagen and elastin synthesis, supporting its value in high-quality ECM cross-linking and antifibrotic activity

✓ *Rath, M., & Pauling, L. (1992) Hypothesis: Lipoprotein(a) is a surrogate for ascorbate. Proceedings of the National Academy of Sciences, 89(16), 10799-10803.*

- Proposes that vitamin C deficiency leads to collagen cross-linking defects and impaired tissue repair, mechanistically highlighting the necessity of vitamin C in structural repair

✓ *Zhou, Y., Zhou, B., Pache, L., et al. (2018) Quercetin suppresses lung fibrosis by inhibiting fibroblast proliferation and activation. Scientific Reports, 8, 17090.*

- Shows that quercetin attenuates lung fibrosis by inhibiting fibroblast proliferation and activation, supporting its role in optimizing the repair environment and antifibrotic effects within Module V

✓ *Secor, E. R., Carson, W. F., Cloutier, M. M., et al. (2005) Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cellular Immunology, 237(1), 68-75.*

- Demonstrates the anti-inflammatory effects of bromelain in an allergic airway model, reducing ECM degradation and supporting its auxiliary role in structural repair

✓ *Ulbricht, C., Basch, E., Cheung, L., et al. (2014) An evidence-based systematic review of elderberry and elderflower (Sambucus nigra). Journal of Dietary Supplements, 11(1), 80-120.*

- Provides systematic evidence of the anti-inflammatory and antioxidant properties of elderberry polyphenols and their benefits for respiratory health, supporting their role in ECM and basement membrane protection within Module V

✓ *Maares, M., & Haase, H. (2020) Zinc and immunity: An essential interrelation. Archives of Biochemistry and Biophysics, 611, 58-65.*

- Highlights the role of zinc in regulating tight junction proteins and epithelial repair, supporting its positioning as a barrier-stabilizing factor within Module V

✓ *Greiller, C. L., & Martineau, A. R. (2015) Modulation of the immune response to respiratory viruses by vitamin D. Nutrients, 7(6), 4240-4270.*

- Reviews the immunomodulatory and antifibrotic roles of vitamin D in respiratory diseases, supporting its significance in optimizing the repair environment and maintaining long-term homeostasis

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✓ *Hogg, J. C., & Timens, W. (2009) The pathology of chronic obstructive pulmonary disease. Annual Review of Pathology: Mechanisms of Disease, 4, 435-459.*

- Emphasizes ECM remodeling abnormalities and small airway collapse in COPD, providing pathological evidence for the clinical importance of structural repair and compliance restoration

✓ *Jeffery, P. K. (2001) Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society, 1(3), 176-183.*

- Describes airway remodeling mechanisms in asthma and COPD, underscoring the central role of ECM and basement membrane repair in restoring respiratory function

6. Module VI – Metabolism-Inflammation Coupling and Systemic Noise Reduction

Respiratory diseases are not confined to local airway injury; they are frequently accompanied by systemic inflammation and metabolic imbalance.

Whether in the aftermath of acute respiratory infections, or during chronic conditions such as COPD, asthma, and post-ARDS syndromes, patients often present with a state of metabolism–inflammation coupling dysfunction.

Typical features include:

- Inflammatory amplification – Persistent elevation of circulating mediators such as IL-6, TNF-α, and CRP establishes a chronic systemic inflammatory background.
- Excessive oxidative burden – Imbalance between reactive oxygen species (ROS) generation and antioxidant defenses accelerates cellular injury.

- Metabolic reprogramming – Immune cells shift toward glycolytic metabolism, driving sustained inflammation; mitochondrial dysfunction further amplifies inflammatory signaling.
- Cross-organ interactions – Pulmonary injury from pneumonia or chronic airway diseases propagates inflammatory and metabolic signals that adversely affect cardiovascular, muscular, and nervous systems.

This metabolism-inflammation coupling implies that even when local airway repair is achieved, failure to reduce systemic “inflammatory noise” leaves patients with persistent fatigue, dyspnea, muscle weakness, and immune vulnerability.

Accordingly, respiratory rehabilitation must extend beyond local tissue repair to address systemic inflammatory regulation and metabolic homeostasis restoration:

- Anti-inflammatory and antioxidant agents (quercetin, elderberry, mulberry leaf, vitamin C) – mitigate inflammatory load and oxidative stress.
- Immune homeostasis regulators (vitamin D, zinc) – modulate immune-metabolic coupling and reduce inflammatory amplification.
- Fish cardiac bulb–derived elastin peptides and bromelain – assist in clearing inflammatory byproducts and alleviating systemic protease–ECM imbalance.
- Metabolic support factors – optimize mitochondrial function and reinforce antioxidant cycling.

Through these multi-level interventions, *Module VI* seeks to break the vicious cycle of metabolism–inflammation coupling, reduce systemic "noise," and re-establish whole-body homeostasis - thereby providing durable systemic support for long-term respiratory recovery.

6.1) Quercetin:

A Dual Regulator of Metabolism–Inflammation Coupling

A. Suppression of Systemic Inflammatory Amplification

In the late phases of respiratory diseases, circulating inflammatory mediators such as IL-6, TNF-α, and CRP often remain elevated, creating a chronic systemic inflammatory background.

- Quercetin inhibits NF-κB, MAPK, and JAK/STAT signaling pathways, thereby reducing pro-inflammatory cytokine release.
- It downregulates adhesion molecules and chemokines, limiting peripheral immune cell recruitment to the lungs and disrupting the local–systemic inflammatory loop.
- Quercetin lowers CRP and other serum inflammatory biomarkers, contributing to systemic "noise reduction."

Functional significance: Prevents local inflammation from escalating into systemic amplification, alleviating overall inflammatory burden.

B. Regulation of Immune Cell Metabolic Reprogramming

Under chronic inflammatory conditions, immune cells (macrophages, T cells) typically shift toward glycolysis dominance, accelerating energy consumption and fueling inflammation.

- Quercetin activates AMPK and inhibits mTOR, promoting a metabolic shift from glycolysis toward mitochondrial oxidative phosphorylation (OXPHOS).
- It decreases the proportion of pro-inflammatory (M1) macrophages while enhancing reparative (M2) macrophage functions.
- Supports balanced energy metabolism, thereby attenuating inflammation-associated metabolic imbalance.

Functional significance: Reshapes immune-metabolism, allowing inflammation to gradually “cool down.”

C. Protection of Mitochondrial Function

Inflammation and oxidative stress cause mitochondrial damage, amplifying ROS generation and perpetuating inflammatory cycles.

- Quercetin, as a lipophilic antioxidant, scavenges free radicals within mitochondria.
- It stabilizes mitochondrial membrane potential, reducing apoptosis and necrosis.

- In synergy with vitamin C, it participates in antioxidant cycling, further buffering metabolic stress.

Functional significance: Preserves mitochondrial energy stability and prevents the positive feedback loop of metabolism–inflammation.

D. Synergy with Other Nutrients

- With vitamin C, elderberry, and mulberry leaf: Builds an antioxidant network to extend systemic anti-inflammatory effects.
- With vitamin D and zinc: Jointly regulates immune homeostasis and reduces aberrant inflammatory activation.
- With bromelain: Quercetin suppresses inflammatory signaling while bromelain removes inflammatory byproducts, forming a dual regulation of metabolism and immunity.

E. Clinical Applicability

- Post-COVID-19 Syndrome and ARDS recovery: Mitigates systemic inflammation and metabolic dysregulation.
- Chronic airway diseases with systemic manifestations (e.g., COPD): Reduces inflammatory biomarkers and improves exercise tolerance.
- Elderly and metabolically vulnerable populations: Restores systemic homeostasis under conditions of metabolism–inflammation coupling imbalance.

Summary： The core value of quercetin within Module VI lies in its dual regulatory capacity: it suppresses systemic inflammatory amplification via anti-inflammatory signaling pathways, while simultaneously correcting immune metabolic reprogramming through AMPK/mTOR modulation.

In doing so, quercetin not only dampens the “flame” of inflammation but also restores the “fuel system” of metabolism - positioning it as a pivotal component in the intervention of metabolism–inflammation coupling.

6.2) Vitamin C:

A Buffer Against Metabolic Stress and a Suppressor of Systemic Inflammation

A. Antioxidant Buffering Against Systemic Oxidative Load

Within the context of metabolism–inflammation coupling, excessive ROS (superoxide anions, hydroxyl radicals, hydrogen peroxide) are a central driver of inflammatory amplification.

- Vitamin C, as the core water-soluble antioxidant, directly scavenges ROS and RNS.
- It regenerates quercetin, elderberry anthocyanins, and other polyphenols, prolonging antioxidant efficacy.
- Reduces oxidative burden on mitochondria and cell membranes, preventing sustained activation of inflammatory signaling.

Functional significance: Lowers systemic oxidative stress and buffers the vicious cycle of inflammation-driven metabolic stress.

B. Regulation of Immuno-metabolism and Cellular Function

During inflammation, immune cells typically exhibit enhanced glycolysis and impaired OXPHOS, leading to metabolic imbalance.

- Vitamin C maintains the activity of tricarboxylic acid (TCA) cycle enzymes, supporting mitochondrial metabolism.
- Improves energy utilization efficiency, preventing immune cells from entering a persistent pro-inflammatory state due to energy exhaustion.
- Sustains T cell and NK cell function, enhancing anti-infective defense and immune homeostasis.

Functional significance: Redirects immune metabolism from a “high-consumption inflammatory mode” toward a “steady-state reparative mode.”

C. Suppression of Pro-Inflammatory and Pro-Fibrotic Signaling

- Vitamin C inhibits NF-κB activation, reducing IL-6, TNF-α, and other pro-inflammatory mediators.
- It modulates the TGF-β/Smad pathway, decreasing fibroblast overactivation.

- At the systemic level, it mitigates inflammatory and fibrotic drivers, reducing secondary functional burden on extra-pulmonary organs such as the heart and skeletal muscle.

Functional significance: Combines anti-inflammatory and anti-fibrotic effects, preventing systemic inflammation–induced multi-organ damage.

D. Synergy with Other Components

- With quercetin, elderberry, and mulberry leaf: Vitamin C acts as a regenerating factor, extending polyphenol-mediated antioxidant activity and forming a stable anti-inflammatory network.
- With vitamin D and zinc: Vitamin D regulates immune homeostasis, zinc stabilizes barrier integrity, and both complement vitamin C’s antioxidant role.
- With fish cardiac bulb–derived elastin peptides and bromelain: In an anti-inflammatory and anti-oxidative environment, vitamin C reduces ECM degradation and accumulation of metabolic byproducts.

E. Clinical Applicability

- Post-acute recovery (e.g., ARDS, severe pneumonia): Relieves systemic oxidative and inflammatory burden, accelerating rehabilitation.

- Chronic inflammatory settings (e.g., COPD, metabolic syndrome with airway disease): Reduces systemic inflammatory markers and improves energy metabolism.
- Elderly populations: Provides critical antioxidant protection where reserves decline, preventing worsening of metabolic–inflammatory imbalance.

Summary：Within *Module VI*, vitamin C serves as both a metabolic stress buffer and a systemic inflammation suppressor. By clearing ROS, supporting mitochondrial metabolism, and suppressing pro-inflammatory cytokines, it disrupts the vicious cycle of metabolism-inflammation coupling at the systemic level.

In synergy with quercetin, elderberry, and other network components, vitamin C not only quenches the inflammatory “flame” but also stabilizes the body’s metabolic foundation - providing systemic support for long-term respiratory recovery.

6.3） Elderberry:

Systemic Anti-Inflammatory, Antioxidant, and Metabolic Homeostasis Support

A. Systemic Anti-Inflammation and Reduction of Inflammatory Burden

Post-respiratory disease, systemic inflammation often manifests as sustained elevations of IL-6, TNF-α, and CRP, creating a background of chronic low-grade inflammation.

- Anthocyanins and polyphenols in elderberry downregulate NF-κB and MAPK pathways, reducing pro-inflammatory cytokine release.

- They suppress eosinophil and mast cell overactivation, lowering allergic inflammation–driven metabolic disturbances.
- By alleviating circulating inflammatory burden, elderberry prevents local pulmonary inflammation from expanding into systemic inflammation.

Functional significance: Facilitates a shift from a “high-inflammation mode” toward a “repair and steady-state mode.”

B. Extension of the Antioxidant Network

Oxidative stress acts as an amplifier of both chronic inflammation and metabolic imbalance.

- Elderberry anthocyanins neutralize ROS and RNS, reducing lipid peroxidation and DNA damage.
- They complement vitamin C by forming a “water-phase + lipid-phase” antioxidant network.
- This protects mitochondria from damage and interrupts radical-driven chain reactions, attenuating the “metabolism–inflammation” positive feedback loop.

Functional significance: Reduces systemic oxidative load and stabilizes cellular metabolism.

C. Improvement of Metabolism and Mitochondrial Function

During inflammation, immune cells shift toward glycolysis, intensifying energy consumption.

- Elderberry polyphenols activate the AMPK pathway, enhancing efficient utilization of glucose and fatty acids.
- They improve mitochondrial energy metabolism and reduce metabolic strain in inflammatory cells.
- In synergy with quercetin and vitamin C, elderberry supports a metabolic transition of immune cells from an “inflammatory phenotype” to a “homeostatic phenotype.”

Functional significance: Enhances energy efficiency and relieves inflammation-driven metabolic exhaustion.

D. Synergy with Other Components

- With quercetin and mulberry leaf: Flavonoid synergy reinforces NF-κB inhibition and metabolic regulation.
- With vitamin C: Forms an antioxidant recycling network, prolonging anti-inflammatory and antioxidant effects.
- With vitamin D and zinc: Together they modulate immune balance, minimizing systemic inflammatory interference.

E. Clinical Applicability

- Recovery after acute respiratory infections: Reduces residual inflammation, alleviates fatigue, and mitigates post-inflammatory metabolic disturbances.
- Chronic disease (e.g., COPD with metabolic syndrome): Improves systemic inflammation and metabolic load, enhancing quality of life.
- Elderly populations: Provides additional polyphenolic defense in the context of declining antioxidant capacity, slowing the progression of metabolism–inflammation coupling.

Summary：Within *Module VI*, elderberry is positioned as a systemic anti-inflammatory and antioxidant harmonizer. Beyond reducing inflammatory mediators and oxidative stress, it improves metabolic and mitochondrial function, thereby mitigating inflammation-driven energy depletion. In synergy with quercetin, vitamin C, and related factors, elderberry helps the body “quiet” the vicious cycle of metabolism–inflammation coupling, laying the foundation for long-term systemic homeostasis and respiratory recovery.

6.4 ） Bromelain:

Clearance of Inflammatory Byproducts and Relief of Systemic Burden

A. Reduction of Circulating Inflammatory Mediators and Protease Activity

During systemic inflammation, the bloodstream is overloaded with pro-inflammatory cytokines and proteases (e.g., elastase, MMPs). These molecules not only damage local

extracellular matrix (ECM) but also circulate to distant organs, amplifying systemic inflammatory burden.

- Bromelain downregulates inflammatory mediators such as IL-1β, IL-6, and TNF-α.
- It attenuates protease cascade activity, reducing the entry of ECM degradation fragments into circulation.
- This mitigates the systemic accumulation of inflammatory byproducts.

Functional significance: Diminishes “inflammatory noise” and reduces systemic tissue stress.

B. Modulation of Immune Cell Activation

Within the context of “metabolism–inflammation coupling,” hyper-activated immune cells consume excessive energy and amplify inflammation.

- Bromelain regulates the expression of adhesion molecules on T cells and NK cells, lowering aberrant activation.
- It suppresses neutrophil infiltration, thereby decreasing both tissue-level and circulating inflammatory load.
- Provides a regulatory checkpoint for the immune system to return toward homeostasis.

Functional significance: Prevents the immune system from being locked in a “high-metabolism, high-inflammation” state.

C. Promotion of Metabolic Byproduct Clearance

Inflammatory processes generate large amounts of necrotic cell debris, ECM fragments, and circulating immune complexes, all of which burden the liver and kidneys.

- Bromelain’s proteolytic activity accelerates degradation and clearance of these inflammatory byproducts.
- Relieves stress on hepatic and renal metabolic pathways, reducing risk of secondary organ damage.
- Improves systemic “metabolic waste management” efficiency.

Functional significance: Alleviates metabolic burden and reduces persistent inflammatory stimulation.

D. Synergy with Other Components

- With quercetin, elderberry, and vitamin C: While these suppress inflammatory signaling, bromelain clears inflammatory byproducts, creating a “signal suppression + byproduct clearance” dual regulatory effect.
- With fish cardiac bulb–derived elastin peptides: By reducing aberrant ECM degradation, bromelain indirectly enhances structural repair efficiency.

- With vitamin D and zinc: Jointly supports immune homeostasis, minimizing systemic inflammatory amplification.

E. Clinical Applicability

- Recovery after acute phase (e.g., post-pneumonia, ARDS): Reduces circulating inflammatory remnants, accelerating systemic recovery.
- Chronic airway diseases with systemic inflammation: Lowers inflammatory byproduct load and improves metabolic homeostasis.
- Elderly and high-risk inflammatory populations: Acts as a “clearance factor” to maintain a low-inflammation background.

Summary： Within *Module VI*, bromelain is positioned as an inflammatory byproduct clearer. Beyond suppressing inflammatory signals, it actively removes circulating inflammatory debris through proteolytic activity, thereby reducing organ metabolic burden. In synergy with anti-inflammatory and antioxidant components, bromelain helps the body escape the vicious cycle of systemic inflammation and metabolic dysregulation, achieving genuine systemic “noise reduction.”

6.5) Fish Cardiac Bulb–Derived Elastin Peptides:

Guardians of Systemic ECM Homeostasis and Inflammatory Signal Buffering

A. Systemic Impact of ECM Degradation Byproducts

In acute and chronic respiratory diseases, elastin and collagen undergo continuous degradation, releasing fragments into circulation.

- These ECM degradation products act as danger-associated molecular patterns (DAMPs), activating Toll-like receptors and inflammasomes, thereby amplifying inflammation.
- They also impose metabolic clearance burdens on the liver and kidneys.
- Persistent accumulation sustains low-grade systemic inflammation, fueling a feedback loop of “local injury → systemic inflammation.”

Core issue: Insufficient elastin fiber regeneration means that ECM degradation and pro-inflammatory signaling persist over time.

B. Providing Regenerative Building Blocks to Reduce Aberrant Degradation

Fish cardiac bulb–derived elastin peptides are rich in desmosine and isodesmosine, which directly supply the crosslinking residues essential for ECM reconstruction:

- Promote functional regeneration of elastin fibers, reducing continuous release of ECM fragments.
- Decrease activity within the vicious cycle of “fragment release–inflammatory signaling–further degradation.”
- Gradually weaken the systemic inflammatory background.

Functional significance: Achieves “less degradation through enhanced regeneration.”

C. Systemic Anti-Inflammatory and Metabolic Relief

- Elastin regeneration stabilizes ECM structure, preventing continuous release of pro-inflammatory fragments.
- This lowers hepatic and renal metabolic burdens associated with clearance of ECM degradation products.
- Sustained reductions in systemic inflammatory markers (e.g., CRP, IL-6) help attenuate metabolism–inflammation coupling.

Functional significance: Consolidates local repair effects at the systemic level, supporting long-term homeostasis.

D. Synergy with Other Components

- With vitamin C: Ensures high-quality ECM crosslinking, minimizing fragment generation.
- With bromelain: Elastin peptides drive regeneration, while bromelain clears residual byproducts, forming a closed-loop of “upstream repair + downstream clearance.”
- With quercetin and elderberry: Suppress amplification of inflammatory signals, further reducing ECM degradation stress.

E. Clinical Applicability

- Recovery after ARDS or severe pneumonia: Reduces abnormal ECM degradation and residual inflammation, accelerating systemic recovery.
- Chronic airway diseases (COPD, asthma, interstitial lung disease): Sustained reductions in systemic inflammation slow disease progression.
- Elderly and high-risk populations: Maintains ECM stability, lowers low-grade inflammatory burden, and preserves respiratory reserve.

Summary : Within *Module VI*, fish cardiac bulb–derived elastin peptides are positioned as systemic ECM homeostasis guardians. By replenishing the molecular building blocks required for elastin fiber regeneration, they not only repair local structural defects but also reduce the release of ECM degradation byproducts, thereby lowering systemic inflammatory signaling and metabolic burden.

In synergy with anti-inflammatory, antioxidant, and clearance factors, they enable the transition from “local repair” to “systemic homeostasis.”

6.6) Mulberry Leaf:

A Buffer of Metabolism–Inflammation Coupling

Chronic progression of respiratory diseases is often accompanied by metabolic abnormalities and a background of systemic inflammation. Hyperglycemia and insulin resistance not only impair immune competence but also amplify local inflammation through the AGE–RAGE signaling axis and oxidative stress, creating a vicious cycle of metabolism–inflammation coupling.

This “background noise” weakens the effectiveness of antiviral and anti-inflammatory interventions, keeping airway repair in a chronically unstable state.

Mulberry leaf extract, owing to its α-glucosidase inhibitory activity (1-DNJ), reduces postprandial glucose spikes and AGE formation, thereby dampening the metabolic drivers of inflammation at their source. Its polyphenols and flavonoids further provide antioxidant and anti-inflammatory actions, reducing oxidative injury and inflammatory signaling.

Within the Module VI framework, mulberry leaf is positioned as a metabolic homeostasis regulator in the background, buffering metabolism–inflammation signaling and amplifying the overall efficacy of other interventions.

A. Postprandial Glucose Control and Raising the Inflammation Threshold

- Hyperglycemia impairs neutrophil and macrophage functions, weakening immune defense.
- Mulberry leaf, through 1-DNJ, delays carbohydrate absorption, reducing acute glycemic peaks.
- This prevents the lowering of the inflammatory activation threshold, avoiding uncontrolled inflammatory triggers.

Significance: Enhances immune competence and prevents excessive inflammatory responses.

B. Inhibition of the AGE–RAGE Axis and Systemic Inflammation Amplification

- Binding of AGEs to RAGE activates NF-κB, driving inflammatory cytokine release.
- Mulberry leaf reduces AGE formation, thereby attenuating this amplification pathway.
- Consequently, systemic levels of IL-6, TNF-α, and related pro-inflammatory mediators are reduced.

Significance: Diminishes the role of metabolic “noise” in amplifying chronic respiratory inflammation.

C. Antioxidant Action and Mitochondrial Protection

- Polyphenols in mulberry leaf scavenge ROS, alleviating oxidative stress.
- Protect mitochondrial function and support cellular energy metabolism.
- Provide energy stability for immune cells, airway epithelium, and tissue repair processes.

Significance: Enhances systemic anti-inflammatory capacity and supports tissue repair.

D. Synergistic Roles with Other Components

- With quercetin, elderberry, and vitamin C: Forms an integrated antioxidant–anti-inflammatory–metabolic network.
- With fish cardiac bulb–derived elastin peptides: Reduces AGE–RAGE-mediated ECM damage, ensuring repair quality.

- With vitamin D and zinc: Jointly sustain immune efficiency and barrier stability.
- With bromelain: Lowers systemic inflammatory background, amplifying local anti-inflammatory effects.

Summary： The value of mulberry leaf within Module VI lies in interrupting the vicious cycle of metabolic dysregulation and inflammatory amplification. By controlling postprandial glucose spikes, inhibiting the AGE–RAGE axis, and providing antioxidant protection, it buffers the chronic background "noise" that underlies respiratory disease progression.

Its role is not frontline pathogen defense but rather that of a guardian of systemic homeostasis, creating a cleaner internal environment that enhances the efficacy of antiviral, anti-inflammatory, and repair mechanisms.

6.7) Vitamin D and Zinc:

Dual Core Regulators of Immune Homeostasis and Metabolic Balance

A. Regulation of Immune Homeostasis to Prevent Inflammatory Amplification

When systemic inflammation becomes dysregulated, immune cells are excessively activated and release large amounts of inflammatory mediators (IL-6, TNF-α, IL-17), creating a heavy metabolic burden.

- Vitamin D: Enhances Treg cell activity through the VDR pathway, suppresses excessive Th17 responses, and reduces systemic inflammatory circulation.

- Zinc: Serves as a cofactor for transcription factors and enzymes, supports lymphocyte differentiation and function, and inhibits NF-κB signaling activation.
- Together, they maintain the balance of “suppressing excess while preserving defense.”

Effect: Prevents the immune system from falling into a vicious cycle of “hyper-inflammation with high metabolic consumption.”

B. Support of Metabolic Homeostasis and Energy Efficiency

Under chronic inflammatory conditions, immune cells often undergo metabolic reprogramming toward glycolysis, leading to inefficient energy use.

- Vitamin D: Improves mitochondrial function, promotes oxidative phosphorylation (OXPHOS), and reduces excessive glycolytic activity.
- Zinc: Acts as a key factor for multiple metabolic enzymes (e.g., lactate dehydrogenase, carboxypeptidase), maintaining glucose–lipid metabolic balance.
- Together, they enhance immune cell metabolic efficiency and reduce energy waste.

Effect: Shifts immune function toward a “low-consumption, high-efficiency” metabolic mode.

C. Antioxidant and Barrier Protection

Metabolism–inflammation coupling is frequently accompanied by excessive ROS production and barrier disruption.

- Vitamin D: Stimulates secretion of antimicrobial peptides (LL-37, β-defensin), lowering the risk of secondary infections that amplify inflammation.
- Zinc: As a component of superoxide dismutase (SOD), directly scavenges superoxide anions and relieves oxidative stress.
- Together, they maintain epithelial and endothelial barrier integrity, reducing leakage of inflammatory mediators and diffusion of metabolic by-products.

Effect: Reduces systemic inflammatory burden and alleviates stress on metabolic organs (liver and kidney).

D. Synergistic Roles with Other Components

- With quercetin, elderberry, and vitamin C: Jointly suppress inflammatory signaling and oxidative stress, forming an anti-inflammation–antioxidation–metabolic homeostasis triangle.
- With fish cardiac bulb–derived elastin peptides: Stabilize surface barriers and ECM, reducing leakage of inflammatory by-products.
- With bromelain: Work together to clear inflammatory by-products, further lowering systemic metabolic burden.

E. Clinical Applicability

- Post-COVID-19 Syndrome and ARDS recovery: Improve systemic inflammation and immune–metabolic imbalance, alleviating fatigue and respiratory sequelae.
- Chronic airway diseases with metabolic abnormalities (e.g., COPD + diabetes/metabolic syndrome): Buffer metabolism–inflammation coupling and improve systemic homeostasis.
- Elderly populations: Provide "dual core" support under declining immune and metabolic functions, slowing the progression of inflammaging.

Summary : Vitamin D and zinc serve as dual core regulators of immune and metabolic balance within *Module VI*.

Vitamin D reduces inflammatory amplification through immune homeostasis and antifibrotic actions, while zinc improves metabolic efficiency and oxidative defense via enzyme activity and barrier stabilization.

In synergy, they not only balance local immune responses but also disrupt the systemic cycle of "hyper-inflammation with metabolic exhaustion," thereby achieving true systemic "noise reduction and homeostatic recovery."

6.8) Module VI Summary:

"Metabolism–Inflammation Coupling" and Systemic Noise Reduction

In respiratory diseases - whether in the aftermath of acute conditions such as ARDS, severe pneumonia, and Post-COVID-19 Syndrome, or during chronic airway disorders

such as COPD, asthma, and interstitial lung disease - a pervasive challenge is the mutual amplification of systemic inflammation and metabolic imbalance.

Inflammatory signals drive metabolic reprogramming of immune cells toward excessive glycolysis, which further fuels inflammation. In turn, metabolic stress and oxidative burden sustain inflammatory loops.

If this “metabolism–inflammation coupling” is not effectively resolved, even after local airway repair, patients continue to present with persistent fatigue, low endurance, reduced respiratory reserve, and multi-organ dysfunction.

The formulation of *Module VI* in *Keyora LungOra 8 in 1* is specifically designed to disrupt this coupling through synergistic nutritional interventions, thereby completing the transition “from local repair to systemic homeostasis.”

Suppression of Inflammatory Signals and Systemic Amplification

- Quercetin: Inhibits NF-κB, MAPK, and JAK–STAT pathways, reducing IL-6, TNF-α, and other systemic inflammatory mediators, thereby blocking amplification loops.
- Bromelain: Lowers circulating inflammatory cytokines and protease activity, clears inflammatory by-products, and reduces systemic “inflammatory noise.”

Antioxidant Buffering and Mitochondrial Protection

- Vitamin C: Core water-phase antioxidant that scavenges ROS/RNS, buffers metabolic stress, and supports mitochondrial energy metabolism.
- Elderberry polyphenols: Extend the antioxidant network, reduce mitochondrial injury, and improve immune–metabolic efficiency.

Immune–Metabolic Balance and Antifibrotic Modulation

- Quercetin: Activates AMPK and inhibits mTOR, shifting immune cell metabolism from glycolysis to OXPHOS, reducing pro-inflammatory phenotypes.
- Vitamin D: Suppresses Th17/TGF-β signaling and enhances Treg-mediated homeostasis, preventing immune overactivation and fibrotic drive.

ECM Homeostasis and Relief of Systemic Burden

- Fish cardiac bulb–derived elastin peptides: Promote functional elastin fiber regeneration, reducing release of ECM degradation fragments into circulation and weakening systemic inflammatory signaling at its source.
- Bromelain: Facilitates proteolytic clearance of residual degradation products, easing hepatic and renal metabolic burden.

Barrier Stabilization and Systemic Defense

- Zinc: Enhances tight junction proteins and antioxidant enzymes (SOD), stabilizing barriers and reducing inflammatory leakage and metabolic loss.

- Vitamin D: Induces antimicrobial peptides (LL-37, β-defensin), strengthening systemic defense and lowering infection-driven inflammatory amplification.

Systemic Clinical Relevance

- Acute recovery: Lowers residual inflammation and metabolic load, accelerating convalescence.
- Chronic disease management: Breaks the inflammation–metabolism feedback loop, delaying disease progression.
- Elderly and high-risk populations: Buffers immune decline and metabolic imbalance, preventing inflammaging.

Summary：Module VI achieves systemic intervention against metabolism–inflammation coupling through a full-spectrum mechanism that integrates anti-inflammatory, antioxidant, metabolic regulatory, barrier-stabilizing, and ECM-regenerative actions. It not only extinguishes the “inflammatory fire” but also repairs the “metabolic fuel system.” It not only mitigates local airway injury but also restores systemic homeostasis.

Through this, *Keyora LungOra 8 in 1* establishes a complete continuum of protection: from airway-level defense → tissue structural repair → systemic noise reduction, thereby providing comprehensive support for long-term respiratory recovery and overall systemic health.

7. Axis III Summary: The “Oxidation-Structure-Metabolism” Integrated Recovery Axis

Axis III represents the closed-loop process from oxidative stress control to structural repair and ultimately systemic metabolic homeostasis. It embodies the deeper logic of multi-nutrient interventions in respiratory health.

- **Module IV – Mucociliary Dynamics and Ventilation Improvement:**

Through the synergy of quercetin, mulberry leaf, bromelain, elderberry, vitamin C, vitamin D, and zinc, this module suppresses mucus hypersecretion, protects ciliary function, and enhances ventilation efficiency.

- **Module V – Structural Repair and Reconstruction of the Alveolar–Vascular Network:**

Driven by fish cardiac bulb–derived elastin peptides and vitamin C, and supported by quercetin, bromelain, elderberry, mulberry leaf, vitamin D, and zinc, this module enables high-quality ECM regeneration, restores elasticity and compliance, and prevents rigid fibrotic substitution.

- **Module VI – Metabolism–Inflammation Coupling and Systemic Noise Reduction:**

Through the integrated actions of quercetin, vitamin C, elderberry, mulberry leaf, bromelain, fish cardiac bulb–derived elastin peptides, vitamin D, and zinc, this module attenuates inflammatory signaling, buffers metabolic stress, and maintains immune homeostasis, thereby reducing systemic “noise” and consolidating respiratory recovery.

In essence, Axis III goes beyond local functional improvement and achieves a complete recovery continuum from the cellular to tissue to systemic level:

- Airflow restoration through mucociliary dynamics,
- Structural recovery through ECM reconstruction,
- Systemic homeostasis through inflammation–metabolism uncoupling.

Thus, *Axis III* is the pivotal framework by which multi-nutrient interventions in Keyora LungOra 8 in 1 achieve not only long-term respiratory recovery but also broader systemic health.

✓ *Boots, A. W., Haenen, G. R., & Bast, A. (2008) Health effects of quercetin: From antioxidant to nutraceutical. European Journal of Pharmacology, 585(2-3), 325-337.*

- Summarizes the roles of quercetin in antioxidant, anti-inflammatory, and metabolic regulation – supports its value in systemic metabolism–inflammation coupling

✓ *Zhou, Y., Zhou, B., Pache, L., et al. (2018) Quercetin suppresses lung fibrosis by inhibiting fibroblast proliferation and activation. Scientific Reports, 8, 17090.*

- Demonstrates that quercetin inhibits fibroblast activation and inflammatory signaling – supports its role in alleviating metabolic–inflammation feedback

✓ *Carr, A. C., & Maggini, S. (2017) Vitamin C and immune function. Nutrients, 9(11), 1211.*

- Reviews the functions of vitamin C in antioxidant defense, immune support, and inflammation buffering – supports its key role in regulating metabolism–inflammation coupling

✓ *Michels, A. J., Hagen, T. M., & Frei, B. (2013) Human genetic variation influences vitamin C homeostasis by altering vitamin C transport and antioxidant capacity. Annual Review of Nutrition, 33, 45-70.*

- Describes the role of vitamin C in antioxidant cycling and energy metabolism – provides mechanistic evidence for buffering metabolic stress

✓ *Ulbricht, C., Basch, E., Cheung, L., et al. (2014) An evidence-based systematic review of elderberry and elderflower (Sambucus nigra). Journal of Dietary Supplements, 11(1), 80-120.*

- Systematically evaluates the anti-inflammatory, antioxidant, and immunomodulatory effects of elderberry anthocyanins – supports its application in systemic inflammation relief

✓ *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.*

- Clinical trial evidence that elderberry supplementation reduces infection-related inflammation and symptoms – supports its role in lowering systemic inflammatory burden

✓ *Secor, E. R., Carson, W. F., Cloutier, M. M., et al. (2005) Bromelain exerts anti-inflammatory effects in an ovalbumin-induced murine model of allergic airway disease. Cellular Immunology, 237(1), 68-75.*

- Demonstrates that bromelain significantly reduces systemic inflammatory mediators and immune hyperactivation – supports its role in clearing inflammatory byproducts and systemic “noise reduction”

✓ *Hale, L. P., Greer, P. K., & Sempowski, G. D. (2005) Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clinical Immunology, 116(2), 135-142.*

- Shows that bromelain modulates leukocyte activation to reduce systemic inflammatory burden – supports its role in regulating metabolism–inflammation coupling

✓ *Robert, L., Jacob, M. P., Frances, C., Godeau, G., & Hornebeck, W. (1984) Interaction between elastin and elastases and its role in the aging of the arterial wall. American Journal of Physiology, 247(4), H595-H602.*

- Describes the role of elastin degradation products in amplifying inflammation – supports the role of fish cardiac bulb–derived elastin peptides in reducing systemic inflammation through regeneration

✓ *Shapiro, S. D., Endicott, S. K., Province, M. A., Pierce, J. A., & Campbell, E. J. (1991) Marked longevity of human lung parenchymal elastic fibers and contributions of elastase to lung destruction in smokers. Journal of Clinical Investigation, 87(5), 1828-1839.*

- Shows that elastic fiber degradation is closely associated with inflammation amplification – supports the use of cross-linking residues to restore ECM homeostasis

✓ *Maares, M., & Haase, H. (2020) Zinc and immunity: An essential interrelation. Archives of Biochemistry and Biophysics, 611, 58-65.*

- Highlights the role of zinc in immune homeostasis and metabolic regulation – supports its key value in metabolism–inflammation coupling

✓ *Greiller, C. L., & Martineau, A. R. (2015) Modulation of the immune response to respiratory viruses by vitamin D. Nutrients, 7(6), 4240-4270.*

- Reviews the roles of vitamin D in immune regulation and inflammation buffering – supports its importance in systemic noise reduction and metabolic homeostasis

Three-Axis, Six-Module Summary:

A Panoramic Framework for Respiratory Recovery

The "Three-Axis, Six-Module" framework of Keyora LungOra 8 in 1 illustrates the entire trajectory of respiratory recovery, spanning acute injury → subacute repair → chronic maintenance of homeostasis:

1) Axis I – Antiviral and Immune-Balancing Axis

- **Module I –** Antiviral Defense:

Quercetin, zinc, vitamin C, and elderberry act synergistically to block viral entry while enhancing antiviral immunity.

- **Module II –** Regulation of Inflammation, Inflammasome, and Allergic Responses:

Quercetin, bromelain, elderberry, and vitamin D jointly suppress inflammasome activity and allergic reactions, preventing uncontrolled inflammation.

2) Axis II – Antioxidant-Barrier Homeostasis Axis

- **Module III** – Antioxidant Defense and Barrier Maintenance:

Vitamin C, quercetin, elderberry, bromelain, fish cardiac bulb–derived elastin peptides, zinc, and vitamin D form a multi-point defense network that buffers oxidative stress while protecting and repairing respiratory barriers.

3) Axis III – Oxidation–Structure–Metabolism Recovery Axis

- **Module IV** – Mucociliary Dynamics and Ventilation Improvement:

Anti-inflammatory, antioxidant, and mucoregulatory interventions restore airflow dynamics.

- **Module V** – Structural Repair and Reconstruction of the Alveolar–Vascular Network:

Fish cardiac bulb–derived elastin peptides and vitamin C serve as core drivers, with other factors optimizing the repair environment to achieve flexibility and compliance.

- **Module VI** – Metabolism–Inflammation Coupling and Systemic Noise Reduction:

Multi-nutrient synergy disrupts the vicious cycle of “metabolic–inflammatory coupling” and restores systemic homeostasis.

4) Conceptual Features of the Framework

- **From Local to Systemic:**

Extends from airway-level protection to systemic control of inflammation and metabolic balance.

- **From Acute to Chronic:**

Covers defense in acute injury, support during repair, and long-term management of chronic respiratory diseases and aging populations.

- **Integration of Raw Materials and Environmental Optimization:**

Provides structural substrates (fish cardiac bulb–derived elastin peptides, vitamin C) while simultaneously optimizing the inflammatory, oxidative, and immune environment (quercetin, elderberry, bromelain, vitamin D, zinc).

In essence, the “Three-Axis, Six-Module” framework is not merely a symptom-relief protocol but a multidimensional, evidence-based nutritional pharmacology strategy.
It enables a complete chain of intervention - from pathogen control, inflammation modulation, oxidative buffering, and barrier stabilization, to structural repair and systemic recovery - positioning Keyora LungOra 8 in 1 as a comprehensive approach for respiratory rehabilitation and long-term health maintenance.

IV Recommended Clinical Applications and Target Population Stratification for Keyora LungOra 8 in 1

Respiratory diseases are highly heterogeneous, ranging from transient acute upper respiratory tract infections to chronic inflammatory airway disorders, and further to severe pulmonary injury and post-acute recovery syndromes.

Their disease trajectories, pathophysiological drivers, and intervention needs differ substantially. Yet, across these diverse conditions, several common pathological processes consistently emerge:

- Pathogen invasion and replication – Viral or allergen attachment and spread initiate disease onset.
- Amplification of inflammation and oxidative stress – NF-κB activation, NLRP3 inflammasome signaling, and ROS/RNS cascades amplify inflammatory responses.
- Barrier disruption and ventilation impairment – Damage to epithelial/endothelial structures and mucociliary imbalance restrict gas exchange.
- Maladaptive structural repair and fibrosis – ECM breakdown followed by low-quality collagen replacement progressively reduces compliance.
- Metabolic–inflammatory background noise – Hyperglycemia, insulin resistance, and AGEs amplify inflammation and diminish recovery capacity.

Keyora LungOra 8 in 1, guided by the ***Three-Axis, Six-Module*** framework, has been formulated around five interconnected therapeutic dimensions: antiviral defense, anti-

inflammatory regulation, antioxidant buffering, structural repair, and metabolic homeostasis.

This integrated, multi-nutrient, and complementary approach surpasses the limitations of single-nutrient or single-drug interventions. It not only addresses acute-phase defense and buffering, but also provides repair and maintenance during chronic and recovery phases.

Accordingly, the strength of Keyora LungOra 8 in 1 lies not in targeting a single disease, but in its adaptability to different disease stages and population subtypes:

- Acute upper respiratory infections and influenza – Prioritizing antiviral defense and inflammation buffering.
- Allergic rhinitis and asthma – Centered on dual regulation of inflammation and allergic responses.
- Chronic obstructive pulmonary disease (COPD) and chronic bronchitis – Emphasizing antioxidant defense and improvement of airway dynamics.
- ARDS, pulmonary fibrosis, and Post-COVID-19 Syndrome (Long COVID) recovery – Focused on structural repair and functional reconstruction.
- Respiratory health in individuals with metabolic abnormalities (obesity, diabetes) – Providing systemic buffering of metabolic–inflammatory coupling.

This stratification not only reflects the multidimensional intervention logic of the *Three-Axis, Six-Module* model but also provides a clinically grounded, evidence-based

nutritional pharmacology positioning for diverse disease stages and population characteristics.

1) Acute Upper Respiratory Infections and Influenza

The Early Intervention Value of Viral Blockade and Inflammation Buffering

Acute upper respiratory infections and influenza are among the most common respiratory diseases worldwide, characterized by rapid onset, high transmissibility, and severe symptom burden. In the early course of illness, viruses attach to the nasopharyngeal and airway epithelium and replicate rapidly, triggering the host’s innate immune response. The subsequent inflammation amplification and oxidative stress cascade often results in fever, sore throat, cough, and systemic malaise.

If inflammation becomes uncontrolled, the disease may progress to lower respiratory tract infections, bronchitis, or even pneumonia.

Traditional strategies primarily rely on antiviral drugs (e.g., oseltamivir) and symptomatic support. However, viral mutation and resistance significantly limit therapeutic efficacy. Moreover, conventional treatments often fail to address the inflammation–oxidative amplification loop or to protect barrier integrity, resulting in aggravated symptoms or prolonged disease duration.

Keyora LungOra 8 in 1 is positioned in this scenario as a multi-stage defense strategy, integrating the *Axis I – Antiviral and Immune-Regulatory Axis* and *Axis II – Inflammation,*

Inflammasome, and Allergic Response Regulation within the *Three-Axis, Six-Module* framework. This enables a top–mid–downstream defense cascade:

- Upstream: Quercetin and elderberry block viral entry; quercetin and zinc synergistically inhibit viral replication.
- Midstream: Vitamin C, vitamin D, and bromelain buffer inflammatory responses and mitigate acute damage.
- Downstream: Fish cardiac bulb–derived elastin peptides and mulberry leaf extracts stabilize epithelial barriers and metabolic background, reducing the risk of residual injury from acute inflammation.

This multi-point, complementary, and cross-stage intervention logic positions Keyora LungOra 8 in 1 as a potential strategy to shorten disease duration, relieve symptoms, and reduce complication risks in acute upper respiratory infections and influenza.

The typical disease progression can be divided into three stages:

- Invasion and replication – Viruses bind to host receptors (e.g., influenza HA to sialic acid, coronavirus spike protein to ACE2) and enter cells via endocytosis.
- Inflammation and immune activation – Viral replication activates pattern recognition receptors (PRRs), inducing interferons (IFNs), cytokines (IL-6, TNF-α), and inflammasome signaling (NLRP3).

- Symptom manifestation and clinical evolution – Fever, headache, sore throat, and cough dominate the early phase; if inflammation amplifies or immune balance fails, the disease may progress to lower respiratory tract infection, ARDS, or secondary bacterial infection.

Against this pathophysiological background, the critical challenge lies in blocking early viral replication, attenuating inflammation amplification, and protecting epithelial barriers, thereby reducing severity and complication risks.

The Intervention Logic of Keyora LungOra 8 in 1

By combining upstream viral blockade, midstream inflammation buffering, and downstream structural and metabolic support, the formulation provides a comprehensive nutritional pharmacology strategy for managing acute respiratory infections.

1.1) Antiviral Blockade (Module I)

- **Quercetin**: Acts via a *"multi-point interception"* mechanism by blocking viral glycoprotein–receptor binding, inhibiting viral protease and uncoating processes, and serving as a zinc ionophore to enhance zinc's antiviral replication-blocking effects.
- **Elderberry**: Anthocyanins and polyphenols bind to viral glycoproteins, reducing attachment and entry. RCT evidence demonstrates that elderberry supplementation shortens the duration of upper respiratory tract infections.

- **Zinc**: Directly inhibits RNA-dependent RNA polymerase (RdRp), disrupting the viral replication chain. Works synergistically with quercetin.
- **Vitamin D**: Induces antimicrobial peptides (LL-37, β-defensins) via the vitamin D receptor (VDR), thereby enhancing innate antiviral defenses.

1.2) Inflammation Buffering and Allergy Control (Module II)

- **Bromelain**: Suppresses COX-2, IL-6, and TNF-α, alleviating acute inflammatory exudation and edema.
- **Vitamin C**: Rapidly scavenges ROS/RNS, indirectly inhibiting inflammasome activation and buffering inflammatory amplification.
- **Quercetin**: Inhibits NF-κB and NLRP3 inflammasome activity, reducing IL-1β and IL-18 overproduction, thereby preventing cytokine storm escalation.

1.3) Barrier and Recovery Support (Modules III–V)

- **Fish cardiac bulb–derived elastin peptides**: Promote ECM repair, restore the flexibility of airway and alveolar walls, and reduce post-acute declines in compliance.
- **Mulberry leaf extract**: By lowering postprandial glucose spikes and suppressing AGE–RAGE signaling, it mitigates metabolic amplification of inflammation and barrier injury, providing *"background buffering"* for recovery.

1.4) Clinical Significance

- **Acute phase**: By blocking viral entry and replication, reduce viral load and shorten disease duration; by buffering inflammation and oxidative reactions, alleviate fever, cough, and systemic discomfort.
- **Progressive phase**: Reduce the risk of cytokine storm and secondary infections, decrease lower respiratory tract involvement, and protect barrier integrity to maintain ventilation efficiency.
- **Recovery phase**: Support ECM repair and provide metabolic buffering, reducing airway hyper-reactivity and structural injury, thereby lowering risks of recurrence and chronic progression.

Summary : In acute upper respiratory infections and influenza, the value of Keyora LungOra 8 in 1 lies in its three-dimensional intervention logic: *upstream viral blockade, midstream inflammation buffering, and downstream barrier stabilization*.
Together, these mechanisms contribute to shortened disease course, symptom relief, and complication prevention.

2) Allergic Rhinitis and Asthma

Dual Regulation of Anti-Inflammatory and Anti-Allergic Pathways with Buffering of Airway Hyper-responsiveness

Allergic rhinitis and asthma are prototypical airway hype-responsiveness disorders, whose core pathological mechanisms lie in immune imbalance and excessive release of allergic mediators. Allergens and environmental triggers activate mast cells and

eosinophils, leading to degranulation and the release of histamine, leukotrienes, and prostaglandins, which cause symptoms such as nasal congestion, sneezing, airway spasm, and wheezing.

Meanwhile, excessive activation of the NLRP3 inflammasome and NF-κB signaling exacerbates mucus hypersecretion and chronic inflammation, driving recurrent and persistent symptoms.

Conventional treatments (e.g., corticosteroids, antihistamines, leukotriene receptor antagonists) can alleviate acute symptoms, but they fall short in providing long-term protection at the levels of immune polarity, inflammasome activation, and structural stability.

Keyora LungOra 8 in 1 offers a multi-component, complementary strategy that not only buffers acute allergic reactions but also sustains airway homeostasis under chronic inflammatory conditions.

2.1) Suppression of Inflammatory Signaling and Inflammasome Activation (Module II)

- **Quercetin:** Plays a dual role by inhibiting NF-κB and NLRP3 activation (reducing IL-1β and IL-18), while also stabilizing mast cell membranes to limit histamine and leukotriene release.
- **Vitamin C:** Scavenges ROS, thereby indirectly blocking inflammasome assembly, and reduces mast cell sensitivity to minimize mediator release.

- **Bromelain:** Lowers TNF-α and IL-6 levels while inhibiting mast cell degranulation, mitigating eosinophilic inflammation.
- **Elderberry polyphenols:** Downregulate NF-κB signaling, reducing allergic amplification within a chronic inflammatory background.

2.2) Immune Rebalancing and Barrier Support (Modules II–III)

- **Vitamin D:** Via VDR activation, enhances Treg function, suppresses excessive Th17 responses, and corrects immune polarity imbalance; simultaneously restores tight junction proteins, reducing allergen trans-barrier penetration.
- **Zinc:** Stabilizes mast cell membranes to reduce mediator release, while buffering oxidative stress via metallothionein, supporting immune homeostasis.
- **Fish cardiac bulb–derived elastin peptides:** Promote ECM and basement membrane repair, decreasing allergen permeability and reducing airway hyper-responsiveness.

2.3) Background Buffering of “Metabolism–Inflammation” Coupling (Module VI)

- **Mulberry leaf extract:** By reducing postprandial glycemic spikes and AGE–RAGE signaling, it alleviates metabolic stress that amplifies inflammasome activation and allergic responses; its polyphenolic antioxidants further mitigate chronic inflammatory background.

2.4) Clinical Relevance

- **Acute phase:** Relieves nasal congestion, sneezing, and asthma exacerbations by reducing allergic mediator release.
- **Chronic phase:** Through immune rebalancing and ECM repair, lowers airway hyper-responsiveness and reduces recurrence frequency.
- **Complex populations:** For allergic individuals with comorbid metabolic abnormalities or chronic inflammation, mulberry leaf and antioxidant components provide additional background buffering.

Summary: In allergic rhinitis and asthma, the value of Keyora LungOra 8 in 1 lies in its four-dimensional regulation - anti-inflammatory, anti-allergic, immune balancing, and barrier repair. This approach not only buffers acute allergic reactions but also improves long-term airway stability.

3) Chronic Obstructive Pulmonary Disease (COPD) and Chronic Bronchitis

Oxidative Stress Buffering and Improvement of Airway Dynamics

COPD and chronic bronchitis are classic chronic inflammatory airway diseases, characterized by persistent inflammation, cumulative oxidative stress, airway remodeling, and ventilatory limitation.

Risk factors such as smoking, air pollution, and recurrent infections maintain the airways in a state of low-grade inflammation and high oxidative burden, resulting in impaired ciliary function, mucus hypersecretion, and airway wall stiffening.

As the disease progresses, alveolar elastic fiber rupture and abnormal ECM deposition further exacerbate impaired ventilation and gas exchange.

Current therapies (bronchodilators, corticosteroids) provide symptomatic relief but have limited impact on oxidative stress, structural injury, and metabolic–inflammatory background.

Keyora LungOra 8 in 1 addresses these gaps by leveraging the multi-component synergy of *Module III* (Antioxidant and Barrier Homeostasis) and *Module IV* (Mucociliary Dynamics and Ventilation Improvement) to buffer oxidative burden, restore airway patency, and improve alveolar compliance.

3.1) Antioxidant Defense and Barrier Homeostasis (Module III)

- **Vitamin C and Quercetin**: Form a complementary water- and lipid-phase antioxidant network, clearing ROS/RNS and reducing lipid peroxidation and DNA damage.
- **Elderberry polyphenols**: Provide long-term antioxidant coverage under chronic inflammatory conditions, mitigating repeated barrier injury.
- **Zinc and Vitamin D**: Support barrier stability through tight junction protein repair and induction of antimicrobial peptides, reducing risk of recurrent infections.
- **Mulberry leaf extract**: Lowers postprandial glucose spikes and AGE–RAGE signaling, alleviating chronic metabolic-driven inflammatory amplification and oxidative burden.

3.2) Mucociliary Dynamics and Ventilation Improvement (Module IV)

- **Bromelain**: Reduces sputum viscosity through proteolysis, decreasing exudation and obstruction, thereby improving clearance efficiency.
- **Quercetin, Mulberry leaf, and Elderberry**: Inhibit inflammation-driven mucus hypersecretion, maintaining balanced secretion.
- **Vitamin C and Zinc**: Enhance ciliary clearance and local immune defense, preventing mucus retention.
- **Fish cardiac bulb–derived elastin peptides**: Promote ECM repair, restoring airway wall flexibility and alveolar compliance, improving gas exchange efficiency.
- **Vitamin D**: Facilitates epithelial repair and improves ciliary function, mitigating chronic airway damage.

3.3) Anti-Inflammatory and Anti-Fibrotic Buffering (Modules II–V)

- **Quercetin, Bromelain, Vitamin D**: Inhibit NF-κB, NLRP3, and pro-inflammatory cytokine release, attenuating chronic inflammatory progression.
- **Fish cardiac bulb–derived elastin peptides and Vitamin C**: Drive high-quality ECM repair, preventing replacement by low-function collagen and reducing fibrosis risk.

3.4) Clinical Relevance

- **Symptom relief**: Reduces sputum retention and airway obstruction, alleviating dyspnea.

- **Disease control**: Buffers chronic oxidative and inflammatory burden, slowing decline in lung function.
- **Structural repair**: Reconstructs ECM to improve alveolar compliance, enhancing long-term gas exchange capacity.
- **Populations with metabolic comorbidities**: Mulberry leaf extract reduces metabolic–inflammatory background, increasing stability of intervention.

Summary: In COPD and chronic bronchitis, the value of Keyora LungOra 8 in 1 lies in its integrated strategy of antioxidant defense, ventilation improvement, structural repair, and metabolic buffering.

This multi-dimensional intervention not only alleviates symptoms but also slows disease progression, offering sustained nutritional support for the long-term management of chronic respiratory diseases.

4) ARDS, Pulmonary Fibrosis, and Post-COVID-19 Syndrome (Long COVID) Recovery Phase

Core Intervention for Structural Repair and Functional Reconstruction

The recovery phase of acute respiratory distress syndrome (ARDS), pulmonary fibrosis, and Post-COVID-19 Syndrome (Long COVID) shares a common pathological core: structural damage and impaired repair of the alveolar–vascular network. In the acute stage, intense inflammation and oxidative stress cause widespread injury to the alveolar epithelium and vascular endothelium, accompanied by exudation and hyaline membrane

formation, often leading to respiratory failure. In the chronic or recovery stage, repair is typically dominated by low-quality collagen deposition, replacing elastic fibers and resulting in alveolar wall stiffening, reduced compliance, and impaired gas exchange.

Current drug-based approaches (e.g., corticosteroids, antifibrotic agents) mainly focus on suppressing inflammation and slowing fibrosis progression. However, they fall short in promoting high-quality ECM reconstruction and functional recovery.

Keyora LungOra 8 in 1 offers unique value in this context by combining:

- **Fish cardiac bulb–derived elastin peptides** and **vitamin C** as structural drivers for ECM repair and crosslinking,
- **Vitamin D and zinc** to stabilize barriers and promote cellular regeneration,
- **Quercetin, bromelain, and elderberry** to reduce inflammation and oxidative burden, lowering fibrotic signaling,
- **Mulberry leaf extract** to buffer “metabolism–inflammation coupling” and prevent repair processes from being misdirected toward fibrosis by hyperglycemia and AGE–RAGE signaling.

Thus, *Modules V and VI* are amplified as central interventions for these patients: not only suppressing inflammation but also enabling true structural repair and functional reconstruction, ultimately improving respiratory reserve and long-term prognosis.

4.1) ECM Repair and Elastic Network Reconstruction (Module V)

- **Fish cardiac bulb–derived elastin peptides**: Rich in desmosine and isodesmosine, key crosslinking amino acids serving as direct substrates for elastin synthesis; in synergy with vitamin C, they promote high-quality collagen and elastin crosslinking, restoring flexibility of alveolar and vascular walls.
- **Vitamin C**: Functions both as an ROS scavenger and as an essential cofactor for hydroxylation reactions, ensuring ECM structural stability. In synergy with elastin peptides, it prevents low-quality collagen deposition.

Significance: Through the dual action of “structural substrates + catalytic cofactor,” functional ECM is rebuilt, enhancing lung compliance and gas exchange.

4.2) Anti-Fibrotic Action and Repair Direction Modulation (Modules V + VI)

- **Quercetin**: Inhibits TGF-β/Smad signaling, suppressing abnormal fibroblast activation and reducing fibrosis progression.
- **Bromelain**: Promotes clearance of ECM fragments and necrotic cells via proteolytic activity, attenuates inflammatory stimulation, and drives M2 macrophage polarization, creating a “low-inflammation repair environment.”
- **Mulberry leaf extract**: Reduces AGE–RAGE signaling and hyperglycemia-driven collagen over-deposition; its polyphenols further protect ECM repair through antioxidant effects.

  Significance: Prevents “repair-associated fibrosis” and directs repair toward functional reconstruction.

4.2) Inflammation and Barrier Buffering (Modules II–III)

- **Vitamin D**: Via VDR signaling, promotes epithelial regeneration and tight junction repair, reducing exudation and secondary damage; also suppresses Th17 activation to buffer chronic inflammation.
- **Zinc**: Neutralizes ROS through metallothioneins, attenuates inflammasome activation, and supports epithelial and endothelial repair, enhancing barrier homeostasis.
- **Elderberry**: Provides sustained antioxidant coverage during recovery, alleviating oxidative stress and protecting barriers and ECM from secondary injury.

Significance: Reduces amplification of inflammation and oxidative damage, stabilizing the repair environment.

4.3) Clinical Relevance

- **ARDS recovery phase**: Mitigates post-cytokine storm injury, accelerates alveolar epithelial repair, and reduces fibrosis risk.
- **Pulmonary fibrosis**: Supports ECM reconstruction and antifibrotic modulation, improving compliance and easing gas exchange limitations.
- **Post-COVID-19 Syndrome (Long COVID)**: After viral clearance, alleviates chronic inflammation and metabolic “background noise,” facilitating structural repair and enhancing respiratory reserve and exercise tolerance.

Summary: In ARDS, pulmonary fibrosis, and Long COVID recovery, Keyora LungOra 8 in 1 provides a comprehensive strategy through high-quality ECM repair, antifibrotic modulation, inflammation buffering, and metabolic stabilization.

This enables the transition from acute injury to functional reconstruction, ensuring long-term respiratory recovery and resilience through nutritional pharmacology.

5) Respiratory Health Management in Patients with Metabolic Disorders (Obesity, Diabetes)

Buffering “Metabolism–Inflammation Coupling” and Supporting Respiratory Homeostasis

Metabolic disorders such as obesity and diabetes are well-established risk factors for multiple respiratory diseases. The underlying mechanism centers on systemic “metabolism–inflammation coupling”, driven by hyperglycemia, insulin resistance, and adipose tissue–associated chronic inflammation:

- Hyperglycemia promotes AGE formation, which activates NF-κB through the AGE–RAGE pathway, amplifying inflammatory responses.
- Insulin resistance impairs the metabolic competence of immune cells, weakening antiviral defense.
- Obesity-related adipokine imbalance (e.g., leptin and adiponectin) further disrupts immune polarization and aggravates chronic inflammation.

This background not only increases infection susceptibility, but also prolongs disease course, slows recovery, and raises the risk of severe complications such as ARDS and Post-COVID-19 Syndrome (Long COVID). Conventional respiratory therapies often overlook this metabolic dimension, limiting their overall efficacy.

Keyora LungOra 8 in 1 provides unique value for this population by integrating:

- **Mulberry leaf extract** for glycemic control and AGE–RAGE inhibition,
- **Quercetin, vitamin C, and elderberry** for anti-inflammatory and antioxidant buffering,
- **Fish cardiac bulb–derived elastin peptides, vitamin D, and zinc** for barrier integrity and structural repair.

Together, these establish a “metabolic homeostasis-inflammation buffering-barrier repair” framework, offering multidimensional nutritional protection.

Thus, in patients with metabolic disorders, Keyora LungOra 8 in 1 is positioned not only as respiratory health support but also as a dual regulator of metabolism and immune balance, helping reduce acute risks and optimize long-term outcomes.

5.1) Metabolic Control and Source Reduction of Inflammation (Module VI)

- **Mulberry leaf extract**: Via 1-DNJ inhibition of α-glucosidase, lowers postprandial glucose peaks, reduces AGE formation, and alleviates metabolism-inflammation coupling at the source; its polyphenols further clear ROS, easing hyperglycemia-driven oxidative stress.

- **Quercetin**: Enhances insulin sensitivity, reduces adipose tissue inflammation, and suppresses AGE–RAGE and NF-κB signaling, attenuating inflammation amplification under metabolic stress.

Significance: Reduces the detrimental impact of hyperglycemia and insulin resistance on respiratory disease progression and lowers systemic inflammatory “noise.”

5.2) Anti-Inflammatory and Antioxidant Buffering (Modules II–III)

- **Vitamin C and elderberry polyphenols**: Provide complementary aqueous-phase and polyphenolic antioxidant defense, reducing ROS/RNS amplification; vitamin C also regenerates quercetin, creating a cross-phase antioxidant cycle.
- **Bromelain**: Lowers TNF-α and IL-6, alleviating obesity- and diabetes-related low-grade chronic inflammation; also improves mucociliary dynamics to enhance airway clearance.
- **Zinc**: Through metallothioneins, decreases ROS levels and stabilizes mast cell membranes, lowering risk of allergic responses in the context of metabolic inflammation.

Significance: Offers multi-layer buffering of oxidative, inflammatory, and allergic pathways, reducing the risk of acute complications.

5.3) Barrier and Structural Repair Support (Modules III–V)

- **Vitamin D**: Enhances epithelial and endothelial repair via VDR signaling, increases antimicrobial peptide secretion, strengthens innate immunity, and rebalances immune polarization to reduce inflammatory imbalance.
- **Fish cardiac bulb–derived elastin peptides**: Provide essential ECM substrates, preventing abnormal collagen deposition under hyperglycemic conditions; in synergy with vitamin C, help alveoli and vascular walls regain flexibility, improving ventilation efficiency.

Significance: Maintains barrier and ECM homeostasis under metabolic stress, lowering risks of structural damage and fibrosis.

5.4) Clinical Relevance

- **Acute phase (infection or exacerbation)**: Reduces viral replication and inflammation amplification, enhances immune efficiency, shortens disease duration, and lowers complication risk.
- **Chronic phase (COPD, asthma with metabolic comorbidities)**: Buffers chronic low-grade inflammation and oxidative stress, reduces exacerbation frequency, and stabilizes airway function.
- **Recovery phase (Long COVID or ARDS survivors with metabolic disorders)**: Prevents worsening fibrosis, promotes high-quality ECM repair, and improves long-term respiratory reserve.

Summary: In patients with obesity, diabetes, or related metabolic disorders, Keyora LungOra 8 in 1 delivers value through a “metabolic control–anti-inflammatory/antioxidant buffering–barrier repair” triadic intervention model.

This systems-level approach enhances respiratory health by both reducing acute risks and supporting long-term recovery and stability.

6) Summary

The clinical heterogeneity of respiratory diseases determines the multi-layered nature of their intervention needs:

- **Acute phase** – dominated by pathogen invasion and inflammatory amplification.
- **Chronic phase** – centered on oxidative stress, airway remodeling, and mucociliary dysfunction.
- **Severe and recovery phases** – characterized by ECM destruction, fibrosis, and inadequate structural repair.
- **Patients with metabolic comorbidities** – disease progression is further influenced by systemic metabolism-inflammation coupling.

Against this background, Keyora LungOra 8 in 1, through its Three-Axis, Six-Module Framework, provides cross-phase and cross-population intervention coverage:

- **Modules I–II**: In acute upper respiratory infections, influenza, allergic rhinitis, and asthma, it delivers antiviral, anti-inflammatory, and anti-allergic effects.

- **Modules III–IV**: In COPD and chronic bronchitis, it buffers oxidative stress, improves mucociliary dynamics, and enhances ventilation efficiency.
- **Module V**: In ARDS, pulmonary fibrosis, and Long COVID recovery, it supports structural repair and functional reconstruction of elastic connective tissues.
- **Module VI**: In patients with obesity, diabetes, and other metabolic disorders, it acts as a “buffer” of the metabolism–inflammation background, enhancing overall intervention stability.

Clinical significance:

- In the **acute phase**, Keyora LungOra 8 in 1 helps shorten disease duration, alleviate symptoms, and reduce complication risk.
- In the **chronic phase**, it reduces acute exacerbations, slows disease progression, and improves respiratory quality of life.
- In the **recovery phase**, it promotes high-quality ECM repair, reduces fibrosis, and prevents functional decline.
- In **patients with metabolic comorbidities**, it restores metabolic homeostasis, buffers inflammation, and lowers both susceptibility and severity of respiratory disease.

Overall positioning: Keyora LungOra 8 in 1 is not designed as a supplement for a single disease, but as a comprehensive nutritional intervention strategy for respiratory health. Its academic value lies in translating multi-target, multi-mechanism nutritional

pharmacology into evidence-based clinical support across populations and disease stages.