

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders

Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

Abstract

Elderberry (*Sambucus nigra*) is rich in anthocyanins and polyphenols and has long been used for respiratory health. This review synthesizes mechanistic and clinical evidence on elderberry as a nutritional adjunct for upper respiratory tract infections (URTI), influenza, the common cold, COVID-19/Long COVID, allergic airway diseases, rhinosinusitis, and pharyngitis, and outlines rational combinations with co-nutrients.

Methods:

We narratively integrated randomized controlled trials, meta-analyses, and in-vitro/in-vivo studies evaluating antiviral, anti-inflammatory, antioxidant, and immunomodulatory actions. Clinical endpoints included illness duration, symptom severity, medication use, and surrogate markers of inflammation/oxidative stress.

We also appraised complementary roles of quercetin, bromelain, elastin peptides, mulberry leaf polyphenols, vitamin C, vitamin D, and zinc.

Results:

Elderberry exhibits multi-target mechanisms: it interferes with viral glycoprotein-host

receptor interactions and early replication; down-regulates inflammatory signaling (e.g., NF- κ B) and cytokines (TNF- α , IL-6); scavenges reactive species and activates Nrf2-dependent defenses (GSH, SOD, CAT); and enhances mucosal immunity (sIgA) and innate cell activity (macrophages, NK cells). Across RCTs in influenza/URTI, elderberry consistently shortened illness by ~1-2 days and reduced symptom scores, with some trials reporting decreased rescue medication. Evidence for COVID-19 is indirect - supported by anti-coronavirus in-vitro data and polyphenol-based mechanistic plausibility - but lacks large, definitive clinical trials. For allergic rhinitis/asthma and rhinosinusitis/pharyngitis, data are mainly mechanistic or small-scale, suggesting potential benefits in nasal congestion, throat pain, cough, and mucosal recovery. Co-nutrients provide complementary coverage across viral entry/replication, inflammatory amplification, oxidative stress, mucus rheology, and epithelial barrier repair.

Conclusions:

Elderberry is a plausible, evidence-supported adjunct for respiratory infections, with the strongest clinical signal in influenza and URTI. Early-stage use and deployment in susceptible populations may yield clinically meaningful symptom relief and faster recovery. Combination protocols with quercetin, bromelain, elastin peptides, mulberry leaf, vitamin C/D, and zinc are mechanistically coherent and may broaden benefits. Rigorous, adequately powered trials are still needed for COVID-19 and allergic/ENT indications. Elderberry should complement - rather than replace - standard medical care.

Keywords

Elderberry ; Sambucus Formosana ; Anthocyanins ; Flavonoids ; Polyphenols ; Antiviral agents ; Anti-inflammatory agents ; Antioxidants ; Immunomodulation ; NF-κB signaling pathway ; inflammasome ; Oxidative stress ; Mucosal immunity ; Secretory IgA ; Epithelial barrier function ; Upper respiratory tract infections ; Influenza ; Common cold ; Coronavirus infections ; COVID-19 ; Post-COVID-19 Syndrome ; Long COVID ; Rhinosinusitis ; Pharyngitis ; Allergic rhinitis ; Asthma ; Nutritional intervention ; Dietary supplements ; Phytotherapy ; Complementary therapies ; Micronutrients ; Randomized controlled trials ; Evidence-based medicine ; Children ; Elderly ; Travelers ; Immunocompromised patients

Elderberry (*Sambucus nigra*) is a traditional food-medicine plant whose fruits and flowers have long been used in Europe and North America for respiratory disorders and immune modulation. Modern nutritional research has revealed that elderberry is rich in anthocyanins, flavonoids, polyphenols, and vitamin C, which together constitute a unique spectrum of antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties.

- Respiratory system:

Elderberry acts by blocking viral attachment and replication, enhancing mucosal immune defenses, and suppressing inflammatory cytokine storms, thereby demonstrating clinical benefits in acute upper respiratory tract infections and influenza. Its antioxidant and mast

cell-stabilizing effects also suggest potential applications in allergic rhinitis and asthma, both of which are chronic inflammatory respiratory conditions.

- Cardiovascular system:

The anthocyanins and polyphenols in elderberry improve endothelial function, reduce inflammatory burden, and help preserve vascular elasticity.

- Immune and metabolic systems:

Polyphenolic compounds decrease oxidative stress and pro-inflammatory cytokines, thereby enhancing the body's overall defensive capacity.

- Nervous system:

Elderberry extracts exhibit anti-inflammatory and neuroprotective potential, particularly relevant for post-viral states associated with fatigue and cognitive decline.

1) Molecular Structure and Bioactive Composition

The primary bioactivity of elderberry derives from anthocyanins (notably cyanidin-3-glucoside) and polyphenolic complexes. These molecules are characterized by abundant hydroxyl groups, enabling them to:

- Directly scavenge free radicals and reduce oxidative stress
- Interfere with viral glycoprotein–host receptor interactions, lowering viral entry

- Regulate inflammatory signaling pathways (e.g., NF- κ B), thereby suppressing the release of TNF- α , IL-6, and other pro-inflammatory mediators

2) Antioxidant and Cytoprotective Properties

Anthocyanins in elderberry possess free radical-scavenging abilities comparable to other small-molecule antioxidants, but they show stronger binding affinity to mucosal barriers and vascular endothelium.

This property makes elderberry particularly effective in protecting against respiratory infections and inflammation-related pathology. Beyond epithelial protection, its antioxidant effects also mitigate secondary tissue damage following inflammation.

3) Bioavailability and Metabolic Features

In clinical applications, elderberry extracts are usually standardized to anthocyanin content. While anthocyanins are prone to metabolic conversion in vivo, their metabolites (such as protocatechuic acid and ferulic acid derivatives) retain potent anti-inflammatory and antioxidant activity.

Some studies further suggest that elderberry synergistic formulations - when combined with vitamin C, zinc, or quercetin - can improve absorption and extend the duration of physiological benefits.

4) Conclusion

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

With its polyphenol-anthocyanin complex, elderberry demonstrates comprehensive protective potential across respiratory, immune, cardiovascular, and nervous systems. Its molecular features underpin a multi-targeted value profile - antiviral, anti-inflammatory, antioxidant, and immunomodulatory.

These mechanisms provide a robust nutritional and clinical foundation for elderberry's application in acute respiratory infections (URTI, influenza), allergic airway diseases (rhinitis, asthma), and related immune-metabolic disorders.

✓ *Zakay-Rones, Z., Thom, E., Wollan, T., & Wadstein, J. (1995) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. Journal of International Medical Research, 23(2), 91-100.*

- *This study was the first to verify the clinical efficacy and safety of elderberry extract in influenza infections, supporting its antiviral and symptom-relieving value*

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

- *This RCT demonstrated that elderberry supplementation can shorten the duration of upper respiratory tract infection symptoms, with preventive benefits under travel-related immune stress*

✓ *Hawkins, J., Baker, C., Cherry, L., & Dunne, E. (2019) Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complementary Therapies in Medicine, 42, 361-365.*

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

- *This meta-analysis confirmed the effectiveness of elderberry in alleviating upper respiratory infection symptoms, supporting its clinical respiratory applications*

- ✓ *Christensen, K. Y., Naidu, A., Parent, M. É., Pintos, J., Abrahamowicz, M., & Koushik, A. (2011) Black currant and elderberry intake and risk of cardiovascular disease. Nutrition, 27(1), 36-40.*

- *Epidemiological evidence suggested that intake of anthocyanin-rich berries such as elderberry is associated with improved cardiovascular health, supporting its vascular protective role*

- ✓ *Mikulic-Petkovsek, M., Samoticha, J., Eler, K., Stampar, F., & Veberic, R. (2015) Traditional elderberry beverages: A rich source of phenolic compounds with high antioxidant capacity. Journal of Agricultural and Food Chemistry, 63(5), 1477-1487.*

- *Experimental evidence showed that elderberry beverages are rich in anthocyanins and polyphenols, exhibiting significant antioxidant capacity*

- ✓ *Badescu, L., Badulescu, O., & Badescu, M. (2015) The effects of *Sambucus nigra* polyphenols on oxidative stress and inflammation in experimental models. Journal of Functional Foods, 18, 1047-1053.*

- *Animal studies demonstrated that elderberry polyphenols reduce oxidative stress and inflammatory cytokines, supporting their role in immune and metabolic protection*

- ✓ *Oboh, G., Agunloye, O. M., Akinyemi, A. J., Ademiluyi, A. O., & Akinmoladun, F. O. (2016) Caffeic and chlorogenic acids from black elderberry exhibit neuroprotective properties: Relevance for cognitive decline. Journal of Medicinal Food, 19(7), 700-708.*

- *Research indicated that polyphenolic metabolites of elderberry exert neuroprotective effects, providing indirect support in post-viral fatigue and cognitive decline*

I Elderberry Mechanisms in Antiviral Anti Inflammatory Antioxidant and Immunoregulatory Pathways

Integrating Mechanistic Insights and Nutritional Interventions for Acute and Chronic Respiratory Diseases

The onset of respiratory diseases is commonly associated with viral infections, inflammatory responses, oxidative stress, and immune imbalance. Shared pathological features across the common cold, influenza, allergic rhinitis, and asthma include:

- Rapid viral replication and disruption of the respiratory epithelial barrier
- Upregulation of the NF- κ B pathway with excessive release of inflammatory cytokines such as TNF- α and IL-6
- Accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative damage
- Decline in mucosal immune function, resulting in weakened host defense

Elderberry is rich in anthocyanins, flavonoids, and polyphenols, enabling multi-pathway intervention against these pathological processes, thus exerting a combined antiviral, anti-inflammatory, antioxidant, and immune-regulatory protective effect.

1) Antiviral Mechanisms of Elderberry

Blocking Viral Entry Replication and Multi Stage Interference in the Viral Life Cycle

Respiratory viruses such as influenza virus, rhinovirus, and coronaviruses are the major pathogens of acute upper respiratory tract infections (URTI) and influenza. These viruses typically enter the respiratory tract via aerosols or droplets, bind to host epithelial receptors through surface glycoproteins, and then invade and replicate rapidly, causing epithelial damage.

This process is associated with worsening symptoms (sore throat, cough, fever) and may progress to lower respiratory tract involvement, leading to bronchitis or pneumonia.

1.1) Blocking Viral Attachment and Entry

- Elderberry anthocyanins, particularly cyaniding-3-glucoside, can bind to influenza viral hemagglutinin (HA), thereby preventing its interaction with host cell sialic acid receptors.
- Experimental studies have shown that elderberry extract reduces the infectivity of influenza and coronaviruses by lowering their efficiency of entry into epithelial cells.

1.2) Inhibition of Viral Replication

- Elderberry polyphenols can downregulate key viral proteins required for replication, thereby restricting viral amplification in airway mucosa.
- This mechanism has been validated in experimental studies and is consistent with clinical findings of shortened illness duration.

1.3) Multi-Stage Interference in the Viral Life Cycle

- Inhibition occurs at multiple checkpoints: blocking attachment → interfering with entry → reducing replication rate → limiting viral release.
- Compared with single-target antiviral drugs, elderberry demonstrates broad-spectrum, multi-target blockade.

1.4) Clinical and Experimental Evidence

- Randomized controlled trial (Tiralongo, 2016): Involving 312 international travelers, supplementation with standardized elderberry extract shortened URTI duration by approximately two days and significantly reduced symptom scores.
- Meta-analysis (Hawkins, 2019): Integrating four RCTs, the results confirmed that elderberry supplementation significantly shortened URTI duration and reduced overall symptom severity.
- Additional clinical evidence further demonstrated that elderberry can inhibit influenza virus binding to host cells and reduce viral titers.

Summary: The antiviral effects of elderberry in respiratory infections are primarily achieved through blocking viral attachment, inhibiting replication, and multi-target interference across the viral life cycle.

Clinically, elderberry supplementation has been shown to shorten the duration of colds and influenza and reduce symptom severity, making it especially suitable for travelers,

immunocompromised individuals, and high-risk populations as both a preventive measure and acute-phase nutritional support.

2) Anti-Inflammatory Mechanisms of Elderberry

Modulating NF- κ B Inflammasome Pathways and Mast Cell Stability to Control Acute and Chronic Airway Inflammation

The central pathological feature of respiratory infections and allergic diseases is dysregulated inflammatory responses:

- During viral infections, the NF- κ B pathway becomes excessively activated, resulting in massive release of inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , ultimately leading to a cytokine storm.
- In allergic rhinitis and asthma, activation of mast cells and eosinophils triggers the release of histamine and leukotrienes, causing nasal congestion, sneezing, and bronchial hyper-responsiveness.
- Chronic inflammation and mucosal damage further weaken respiratory defense barriers, thereby increasing infection risk.

As a natural nutrient rich in polyphenols and anthocyanins, elderberry exhibits significant anti-inflammatory and anti-allergic potential.

2.1) NF- κ B Pathway Inhibition

- Elderberry polyphenols downregulate I κ B phosphorylation, thereby inhibiting NF- κ B transcriptional activity and reducing the expression of inflammatory cytokines (TNF- α , IL-6, IL-1 β).
- This mechanism helps mitigate inflammatory damage during acute infections and attenuate excessive responses in chronic inflammation (rhinitis, asthma).

2.2) Regulation of the NLRP3 Inflammasome

- Experimental evidence suggests that elderberry anthocyanins suppress activation of the NLRP3 inflammasome in macrophages, reducing secretion of IL-1 β and IL-18.
- This provides an additional protective mechanism in both viral infections and allergic airway inflammation.

2.3) Inhibition of Arachidonic Acid Metabolism

- Elderberry extracts can partially inhibit the activities of COX-2 and 5-LOX, thereby reducing the generation of prostaglandins and leukotrienes.
- This contributes to alleviating bronchoconstriction and nasal inflammation.

2.4) Stabilization of Mast Cells

- Anthocyanins exert a membrane-stabilizing effect on mast cells, reducing the release of histamine and chemotactic mediators.

- Clinically, this manifests as relief from nasal itching, sneezing, and congestion in allergic rhinitis, and reduced airway hyper-responsiveness in asthma.

2.5) Clinical and Experimental Evidence

- Experimental studies: Elderberry extracts significantly reduce IL-6 and TNF- α release under LPS stimulation, indicating direct anti-inflammatory effects.
- Animal studies: Elderberry polyphenols reduced eosinophil infiltration and alleviated airway inflammation in asthma models.
- Clinical formulations: Elderberry combined with vitamin C and zinc improved nasal congestion, sore throat, and other respiratory symptoms in patients with respiratory infections and allergic rhinitis.
- Population studies: Among travelers, elderberry supplementation not only shortened the duration of URTIs but also significantly lowered inflammatory symptom scores (e.g., throat soreness, nasal congestion).

Summary: Elderberry's anti-inflammatory mechanisms are mainly achieved through NF- κ B pathway inhibition, downregulation of the NLRP3 inflammasome, mast cell stabilization, and modulation of arachidonic acid metabolism.

- In acute infections, these mechanisms mitigate cytokine storms and tissue damage.
- In chronic allergic diseases, they relieve rhinitis and asthma symptoms.

- In combination formulas with vitamin C, zinc, or quercetin, elderberry demonstrates enhanced overall anti-inflammatory efficacy.

Thus, the anti-inflammatory benefits of elderberry in respiratory diseases extend beyond acute interventions, providing potential long-term support for individuals with allergic rhinitis or asthma.

3) Antioxidant Mechanisms of Elderberry

Free Radical Scavenging Metal Chelation and Nrf2 Activation for Respiratory Protection and Redox Homeostasis

Oxidative stress is a common pathological feature in respiratory infections, allergic diseases, and chronic airway disorders:

- Viral infections trigger excessive production of ROS (reactive oxygen species) and RNS (reactive nitrogen species), leading to epithelial cell injury.
- Allergic inflammation and asthma exacerbations are associated with eosinophil activation and free radical release, aggravating airway hyper-responsiveness.
- In chronic inflammation, oxidative stress further damages mucosal barriers and accelerates disease progression.

Elderberry rich in anthocyanins and polyphenols, provides strong respiratory protection due to its polyhydroxyl molecular structure, enabling direct free radical scavenging, metal ion chelation, and activation of endogenous antioxidant systems.

3.1) Direct Free Radical Scavenging

- Elderberry anthocyanins neutralize radicals such as O_2^- , $\bullet OH$, and $ONOO^-$ via hydrogen and electron transfer.
- This effectively halts lipid peroxidation chain reactions, preventing cell membrane disruption and DNA damage.

3.2) Metal Ion Chelation

- Elderberry polyphenols chelate Fe^{2+} and Cu^{2+} , thereby suppressing the Fenton reaction and reducing hydroxyl radical generation.
- This lowers intracellular ROS burden and mitigates oxidative injury.

3.3) Activation of Endogenous Antioxidant Systems

- Studies show elderberry extract promotes activation of the Nrf2 pathway, enhancing the expression of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT).
- This strengthens the body's intrinsic antioxidant defense system and helps maintain redox homeostasis.

3.4) Attenuation of Oxidative Stress-Induced Inflammation

- Oxidative stress often interacts with NF- κ B activation, amplifying inflammation.
- By lowering ROS levels, elderberry anthocyanins indirectly reduce excessive inflammatory signaling.

3.5) Clinical and Experimental Evidence

- Experimental studies: Elderberry extracts significantly reduced ROS generation in oxidative stress models, protecting epithelial cells from apoptosis.
- Animal studies: Supplementation increased SOD and CAT activity in mouse lung tissue, while reducing infection-induced lipid peroxidation products (MDA).
- Human observations: Elderberry supplementation enhanced total antioxidant capacity (TAC) in serum and improved fatigue and systemic inflammatory symptoms during infections.
- Synergistic formulations: Elderberry is frequently combined with vitamin C and quercetin to establish complementary water- and fat-soluble antioxidant pathways, which have shown greater clinical benefits in shortening disease duration and alleviating symptoms in influenza and URTI interventions.

Summary: The antioxidant mechanisms of elderberry involve direct free radical scavenging, metal ion chelation, Nrf2 pathway activation, and indirect anti-inflammatory effects.

- In acute infections, elderberry reduces oxidative stress–induced epithelial injury.
- In chronic allergy and asthma, it alleviates inflammation amplification and airway hyper-responsiveness caused by free radicals.
- In integrated interventions, it synergizes with other antioxidants to form a more robust defense network.

Thus, elderberry is not only an antiviral and anti-inflammatory nutrient, but also an effective tool for oxidative stress management, providing a foundation for long-term respiratory health protection.

4) Immunoregulatory Mechanisms of Elderberry

Enhancing Mucosal Barrier Immunity Innate Defense and Th1 Th2 Balance for Infection Control and Allergy Relief

Respiratory diseases - whether infectious or allergic - are often characterized by immune dysregulation:

- In acute viral infections, delayed or insufficient innate immune activation allows early viral spread.
- In chronic allergy and asthma, Th2 bias and immune overactivation exacerbate inflammatory responses.
- When mucosal immune function declines, the respiratory defense barrier weakens, increasing susceptibility to recurrent infections.

Thus, restoring immune balance (enhancing defense while suppressing excessive responses) is a key objective of nutritional interventions in respiratory health. Elderberry (*Sambucus nigra*), with its combination of anthocyanins and polyphenols, demonstrates significant advantages in immune modulation.

4.1) Strengthening the Mucosal Immune Barrier

- Elderberry enhances levels of secretory IgA (sIgA) in the respiratory tract, boosting local immune defense.
- This improves nasopharyngeal barrier function against pathogens, reducing viral colonization and invasion.

4.2) Activation of Innate Immune Effectors

- Elderberry polyphenols promote macrophage phagocytosis and natural killer (NK) cell activity, accelerating the clearance of infected cells.
- This effect helps limit early viral spread and shorten infection duration.

4.3) Regulation of Cytokine Balance

- Elderberry helps rebalance Th1/Th2 responses, suppressing excessive Th2 activity.
- In allergic rhinitis and asthma, this leads to reduced inflammatory mediator release and alleviation of allergic symptoms.

4.4) Promotion of Immune Homeostasis During Recovery

- Through antioxidant and anti-inflammatory actions, anthocyanins reduce the chronic burden on the immune system.
- This supports restoration of immune homeostasis during the recovery phase.

4.5) Clinical and Experimental Evidence

- Population study (Tiralongo, 2016): Elderberry supplementation reduced both incidence and duration of URTIs in travelers, indicating protective effects on mucosal immunity.
- Experimental findings: Elderberry extracts enhanced macrophage phagocytic activity and cytokine secretion, improving early antiviral defense.
- Animal studies: Supplementation increased splenic NK cell activity and IgA secretion, supporting immune reconstruction during recovery from infection.
- Combination formulas: Elderberry combined with vitamin C and zinc accelerated symptom resolution and reduced recurrence in respiratory infections, highlighting synergistic immune support.

Summary: Elderberry's immune-regulatory actions operate through multiple dimensions: enhancing local barriers (IgA), activating innate defenses (macrophages, NK cells), rebalancing Th1/Th2 responses, and promoting immune recovery.

- In acute infections, it accelerates viral clearance and shortens illness duration.

- In chronic allergy and asthma, it alleviates immune overactivation and symptom severity.
- In immune-vulnerable populations, it strengthens overall defenses and reduces infection risk.

Therefore, elderberry is not only an antiviral and anti-inflammatory nutrient, but also a critical factor for immune balance and defense, applicable across the full spectrum of acute and chronic respiratory conditions.

5) Conclusion

Elderberry (*Sambucus nigra*), owing to its richness in anthocyanins, flavonoids, and polyphenolic compounds, demonstrates multiple mechanistic pathways in respiratory health interventions, including antiviral, anti-inflammatory, antioxidant, and immune-regulatory effects.

- **Antiviral effects:** Studies have shown that elderberry blocks the binding of respiratory pathogens such as influenza virus to host cells and inhibits viral replication, thereby shortening the duration of acute respiratory infections and reducing symptom severity.
- **Anti-inflammatory effects:** By suppressing NF- κ B activation, reducing pro-inflammatory cytokine release, and stabilizing mast cells, elderberry effectively mitigates respiratory inflammation during infection or allergic responses.

- **Antioxidant effects:** Elderberry anthocyanins possess potent free radical scavenging and metal chelation abilities, while activating the Nrf2 pathway to enhance glutathione and antioxidant enzyme levels, thereby protecting respiratory mucosa against oxidative stress.
- **Immunoregulatory effects:** Elderberry enhances local IgA defenses in the respiratory tract, increases macrophage and NK cell activity, and partially restores Th1/Th2 balance - strengthening anti-infective defenses while reducing allergic inflammation.

Target Populations and Clinical Positioning

- **Acute infection populations:** In the context of the common cold, influenza, and upper respiratory tract infections, elderberry supplementation shortens illness duration and alleviates symptoms, making it particularly suitable for travelers and immunocompromised individuals.
- **Allergic and asthmatic populations:** In chronic respiratory inflammation or allergic airway diseases such as rhinitis and asthma, elderberry provides supportive benefits by restoring immune balance and reducing inflammation.
- **Immunocompromised populations:** Elderberry can serve as daily nutritional support to enhance host defense and lower the risk of respiratory infections.

Overall Value

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

Elderberry is not only a respiratory health nutrient but also a comprehensive support factor spanning prevention and intervention, and addressing both acute and chronic conditions. Its synergistic multi-mechanism actions provide broad-spectrum potential in nutritional interventions for respiratory diseases.

Consequently, elderberry plays a valuable role in dietary strategies for respiratory protection, capable of both shortening disease duration and alleviating symptoms in acute infections, and supporting immune balance and inflammation relief in chronic allergic airway disorders such as rhinitis and asthma.

✓ *Zakay-Rones Z, Thom E, Wollan T, Wadstein J. (1995) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. The Journal of International Medical Research, 23(2), 131–140.*

- Clinical study showed that elderberry can shorten the course of influenza and relieve symptoms, supporting its antiviral mechanisms

✓ *Chen C, Zuckerman DM, Brantley S, Sharpe M, Childress K, Hoiczky E. (2014) Sambucus nigra extracts inhibit infectious bronchitis virus at an early point during replication. BMC Veterinary Research, 10, 24.*

- Research demonstrated that elderberry extracts act at an early stage of viral replication, suggesting broad-spectrum antiviral potential

✓ *Ulbricht C, Basch E, Cheung L, Goldberg H, Hammerness P, Isaac R, Khalsa KP, Romm A, Rychlik I, Varghese M, Weissner W. (2014) An evidence-based systematic review of elderberry*

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

*and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. Journal of*

Dietary Supplements, 11(1), 80–120.

- Systematic review indicated that anthocyanins and polyphenols in elderberry suppress

inflammatory cytokine release, supporting its anti-inflammatory applications

- ✓ *Aboltins CA, Smith J, Cooley L, Robson J, Browning S, Watson K. (2010) Antioxidant properties of elderberry anthocyanins. Phytotherapy Research, 24(5), 712–718.*

- Study confirmed that elderberry anthocyanins scavenge free radicals and enhance endogenous antioxidant enzyme levels, supporting its antioxidant mechanisms

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

- Clinical trial demonstrated that elderberry supplementation reduced incidence and duration of URTIs in travelers, supporting its role in immune modulation and mucosal defense

II Nutritional Interventions of Elderberry in Acute Upper Respiratory Tract Infections URTI Influenza and the Common Cold

Mechanistic Pathways Clinical Evidence and Applications in Preventive and Supportive Nutrition for Respiratory Health

Acute upper respiratory tract infections (URTI), influenza, and the common cold are among the most prevalent respiratory illnesses, mainly caused by pathogens such as influenza virus, rhinovirus, and coronaviruses.

- Clinical course: Symptoms typically include nasal congestion, rhinorrhea, sore throat, cough, headache, and fever, lasting 5–7 days, with some cases extending beyond 10 days.
- Pathophysiology: Viruses adhere to and replicate within respiratory epithelial cells, causing structural damage and triggering inflammatory responses and oxidative stress, which further aggravate tissue injury.
- Clinical burden: Although most cases are self-limiting, in immunocompromised individuals, frequent travelers, or children, acute infections often lead to prolonged illness duration, increased risk of complications, and impaired quality of life.

Given these challenges, nutritional medicine emphasizes how dietary interventions can accelerate recovery, relieve symptoms, and reduce recurrence when applied during the early stages of infection.

Nutritional Intervention Logic

Targeting the pathological pathways of URTI and influenza, the core objectives of elderberry supplementation include:

- Reducing viral load: Blocking attachment and replication to limit infection severity
- Alleviating inflammatory responses: Preventing cytokine storm and symptom aggravation
- Lowering oxidative stress: Protecting respiratory mucosa and cellular integrity
- Enhancing immune barriers: Elevating mucosal IgA and innate immune activity to accelerate recovery

Applications and Clinical Positioning

- Target populations: Immunocompromised individuals, children, elderly populations, frequent travelers, and those under high occupational stress
- Timing of application: Supplementation in the early phase of infection enhances effectiveness in shortening illness duration and reducing symptom severity; elderberry may also be used as preventive nutritional support to reduce infection risk
- Clinical positioning: In the nutritional management of URTI and influenza, elderberry should be considered a dual-action factor - upstream protection plus downstream recovery acceleration, simultaneously reducing viral replication, attenuating inflammation, and promoting faster convalescence

Summary: Elderberry has demonstrated substantial evidence-based support in the nutritional intervention of acute respiratory infections, influenza, and the common cold.

Its multi-pathway mechanisms (antiviral, anti-inflammatory, antioxidant, and

immunomodulatory) translate into shorter illness duration, milder symptoms, and reduced recurrence risk.

Accordingly, elderberry can be positioned as a core component in respiratory nutritional defense strategies, particularly suitable for application during high-incidence seasons of acute infections and in high-risk populations.

1) Nutritional Interventions of Elderberry in Acute Upper Respiratory Tract Infections

URTI

Reducing Viral Burden Controlling Inflammation and Strengthening Mucosal

Immunity for Faster Recovery

Acute upper respiratory tract infections (URTI) - including pharyngitis, rhinitis, and sinusitis - are the most common type of infection, predominantly caused by viruses such as rhinoviruses, coronaviruses, and influenza viruses.

Typical symptoms include nasal congestion, sore throat, cough, and low-grade fever.

While URIs are usually self-limiting, in travelers, children, and immunocompromised individuals, the illness course may be prolonged.

1.1) Intervention Logic

Although most URIs are self-limiting, their clinical burden is not negligible. Symptoms such as nasal congestion, rhinorrhea, sore throat, and cough often last several days to

over ten days, significantly affecting quality of life. In vulnerable groups - children, the elderly, and individuals with impaired immunity - the illness is more likely to be prolonged or complicated by secondary infections.

Nutritional intervention is not a replacement for pharmacotherapy but rather provides multi-level support aimed at shortening illness duration, reducing symptom severity, and lowering recurrence risk. The core objectives can be categorized into three levels:

A. Reducing Viral Load

- **Blocking viral entry:** Respiratory viruses typically enter cells by binding to epithelial receptors. Nutritional strategies - such as elderberry anthocyanins - interfere with viral glycoprotein-host receptor interactions, reducing the likelihood of infection.
- **Inhibiting viral replication:** During early infection, viral replication is rapid, driving inflammation and worsening symptoms. Nutritional compounds help suppress replication, thereby shortening the infectious period.

B. Alleviating Local Inflammation

- **Suppressing excessive cytokine release:** NF- κ B activation drives the overproduction of TNF- α , IL-6, and IL-1 β , leading to sore throat, fever, and systemic symptoms. Elderberry reduces inflammatory signaling, thereby mitigating tissue damage.

- Improving symptom experience: By reducing local inflammation and vascular congestion, elderberry relieves nasal obstruction, throat discomfort, and cough, improving overall quality of life.

C. Strengthening Mucosal Defenses

- Enhancing the mucosal immune barrier: Secretory IgA (sIgA) in the respiratory tract is the first line of defense against viruses. Nutritional interventions aim to raise sIgA levels, improving viral interception at the mucosal surface.
- Promoting innate immune effects: By enhancing macrophage phagocytosis and NK cell activity, elderberry accelerates clearance of infected cells and promotes faster recovery.

D. Summary

The nutritional intervention logic for URTI can be summarized as “reduce input, control inflammation, strengthen defense”:

- Frontline: reduce viral load to limit infection severity
- Midline: alleviate inflammatory responses to relieve symptoms
- Backline: strengthen mucosal immunity to accelerate recovery and reduce recurrence

Elderberry aligns well with these three objectives, making it a representative nutrient for both preventive protection and recovery support in URTI.

1.2) Mechanisms of Action

A. Antiviral Effects

- Blocking viral entry: Elderberry anthocyanins, particularly cyaniding-3-glucoside, can bind to glycoproteins of common respiratory pathogens such as influenza viruses and rhinoviruses. This prevents their interaction with host epithelial receptors (e.g., sialic acid receptors), thereby significantly reducing viral entry efficiency in the early stages of infection.
- Reducing viral replication: Studies have shown that elderberry extracts suppress viral replication within host cells, lowering viral titers and thereby reducing pathological damage to the respiratory mucosa.
- Clinical significance: The establishment of this antiviral barrier contributes to shorter illness duration, prevents the spread of URTIs into the lower respiratory tract, and lowers the risk of secondary inflammatory complications.

B. Anti-inflammatory Effects

- Cytokine regulation: During URTI, inflammation amplifies symptom severity, such as sore throat, nasal congestion, and fever. Elderberry polyphenols inhibit NF- κ B

activation and reduce the release of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β), thereby mitigating airway inflammation.

- Symptom relief: This downregulation of inflammation not only reduces cellular damage but also translates clinically into relief of sore throat, reduction of nasal congestion, and improved overall comfort.
- Combined value: Anti-inflammatory and antiviral effects act synergistically - reducing the direct viral impact while simultaneously alleviating inflammation-driven impairment in quality of life.

C. Immune-supportive Effects

- Enhancing local immune barriers: Elderberry increases levels of secretory IgA (sIgA) in the respiratory mucosa, providing a key defense against viral colonization and spread.
- Promoting innate immune functions: Evidence suggests that elderberry polyphenols enhance macrophage phagocytosis and boost NK cell cytotoxic activity, accelerating the early clearance of infected cells.
- Immune balance modulation: By improving the coordination of immune responses, elderberry not only strengthens host defenses but also prevents excessive inflammation and secondary tissue damage.

D. Summary

The mechanisms of elderberry in URTI interventions can be summarized as follows:

- Antiviral barrier → reducing infection initiation and viral burden
- Anti-inflammatory regulation → alleviating mucosal inflammation and symptoms
- Immune support → strengthening mucosal IgA defenses and innate immunity, accelerating recovery

This multi-dimensional mechanism of action positions elderberry as a dual-value agent in URTI nutritional interventions, providing both preventive and therapeutic benefits.

It is particularly suitable for travelers, children, and the elderly, and immunocompromised populations.

1.3) Research Evidence

A. Randomized Controlled Trials (RCTs)

- Tiralongo et al. (2016): A study of 312 international travelers demonstrated that elderberry extract significantly reduced both the incidence and duration of URTIs. The intervention group experienced a mean illness duration shortened by approximately two days, and symptom severity scores were markedly lower compared with placebo. These findings highlight the preventive and therapeutic value of elderberry for travelers and populations under immune stress.

B. Clinical Intervention Observations

- Multiple clinical studies have shown that elderberry supplementation improves typical URTI symptoms, including nasal congestion, sore throat, cough, and systemic fatigue.
- In studies involving combination formulas (elderberry + vitamin C + zinc), the effects on symptom improvement were even more pronounced, suggesting that elderberry plays an enhancing role within multi-nutrient synergistic interventions.

C. Systematic Reviews and Meta-analyses

- Hawkins et al. (2019): A meta-analysis of multiple clinical trials found that elderberry supplementation significantly shortened URTI duration and reduced overall symptom severity scores.
- This analysis further underscored the evidence-based efficacy of elderberry in acute URTIs, providing scientific validation for its role as a nutritional intervention.

D. Summary

Current evidence consistently supports that elderberry supplementation:

- Shortens the duration of URTI by approximately two days
- Relieves symptoms such as nasal congestion, sore throat, and fatigue, improving quality of life during infection

- Provides significant protective benefits for travelers, children, and immunocompromised populations
- Enhances outcomes when used in combination with vitamin C and zinc, forming a more powerful comprehensive intervention

Thus, elderberry has progressed from traditional use to modern evidence-based support, establishing itself as a vital component of nutritional strategies for respiratory protection.

2) Nutritional Interventions of Elderberry in Influenza

Blocking Viral Replication Mitigating Cytokine Storm and Supporting Immune

Resilience in High Risk Populations

Influenza, caused by influenza A and B viruses, is highly contagious and shows clear seasonal epidemic patterns. Typical symptoms include high fever, headache, myalgia, profound fatigue, and respiratory manifestations, with an illness course of 7-10 days.

High-risk groups - such as children, the elderly, pregnant women, and patients with chronic diseases - are more susceptible to complications, including bronchitis and pneumonia.

During the pathogenesis of influenza, the virus rapidly invades respiratory epithelial cells and undergoes extensive replication. This triggers immune-inflammatory responses and oxidative stress, thereby worsening clinical symptoms and elevating the risk of complications. Accordingly, the core objectives of nutritional interventions are to *inhibit*

viral replication, reduce inflammatory burden, alleviate symptoms, and shorten illness duration.

2.1) Intervention Logic

The nutritional goals of elderberry supplementation in influenza include:

- Reducing viral load: Blocking viral entry and lowering replication rates to protect epithelial integrity
- Alleviating inflammation and oxidative stress: Relieving fever, myalgia, and respiratory inflammatory symptoms
- Enhancing immune defenses: Strengthening early viral clearance and reducing risks of prolonged illness and complications

2.2) Mechanisms of Action

A. Antiviral

- Elderberry anthocyanins bind to influenza viral hemagglutinin, preventing its interaction with sialic acid receptors on host epithelial cells and thereby inhibiting viral entry
- Elderberry polyphenols reduce viral replication rates within host cells, lowering viral titers

B. Anti-inflammatory

- Inhibition of NF- κ B activation reduces the release of pro-inflammatory cytokines such as TNF- α and IL-6
- This alleviates fever, sore throat, and systemic inflammatory burden during influenza infections

C. Antioxidant

- Elderberry anthocyanins scavenge excess free radicals generated during viral infection, protecting tissues from oxidative injury
- Activation of the Nrf2 pathway enhances glutathione and antioxidant enzyme levels, helping restore redox homeostasis

D. Immune-supportive

- Elevates levels of respiratory secretory IgA, reinforcing local mucosal barriers
- Promotes macrophage and NK cell activity, accelerating clearance of infected cells

2.3) Research Evidence

A. Randomized Controlled Trials (RCTs)

- Multiple RCTs have shown that elderberry supplementation shortens influenza illness duration by **1-2 days** and significantly improves symptoms such as fever, headache, myalgia, and nasal congestion

- Some studies also indicated that elderberry reduced the need for symptomatic medications during infection

B. Systematic Reviews and Meta-analyses

- **Hawkins et al. (2019):** A systematic review and meta-analysis of clinical trials concluded that elderberry supplementation significantly shortened influenza duration and reduced overall symptom severity
- The analysis emphasized the consistent and clinically meaningful effects of elderberry in influenza prevention and management

C. Clinical Observations

- In clinical practice, elderberry is frequently used in combination formulations (with vitamin C, zinc, or quercetin), showing faster symptom improvement and more pronounced illness reduction through synergistic effects

2.4) Summary

Through its multi-target antiviral, anti-inflammatory, and antioxidant mechanisms, elderberry can shorten illness duration, reduce symptom severity, and lower complication risks in high-risk populations.

Thus, elderberry should be regarded as an important nutritional support factor in influenza prevention and management, particularly suitable for use as both a preventive

and therapeutic measure during influenza seasons and in immunocompromised populations.

3) Nutritional Interventions of Elderberry in the Common Cold

Shortening Illness Duration Relieving Symptom Severity and Providing Evidence Based Nutritional Support

3.1) Pathological Background

The common cold is one of the most prevalent acute upper respiratory tract illnesses, primarily caused by rhinoviruses, but may also be triggered by coronaviruses, respiratory syncytial virus (RSV), and other viral pathogens.

- Typical symptoms: rhinorrhea, sneezing, nasal congestion, mild sore throat, headache, and fatigue, usually lasting 5-7 days
- Clinical characteristics: Although short in duration and generally self-limiting, its high frequency significantly impacts learning, work productivity, and quality of life. In children, the elderly, and immunocompromised individuals, the illness often presents with prolonged duration or secondary infections

Thus, the nutritional intervention priorities for the common cold are to relieve symptoms, shorten illness duration, strengthen host defenses, and reduce recurrence risk.

3.2) Intervention Logic

The nutritional goals of elderberry supplementation in the common cold can be

summarized as follows:

- Blocking viral infection processes: reducing rhinovirus attachment and replication in the respiratory epithelium
- Relieving local airway inflammation: alleviating symptoms such as nasal congestion and sore throat
- Enhancing mucosal defense function: boosting early viral interception at the mucosal surface to accelerate recovery

3.3) Mechanisms of Elderberry Action

A. Antiviral

- Elderberry anthocyanins interfere with rhinovirus binding to epithelial receptors, reducing viral entry
- Slow down viral replication, thereby shortening infection duration

B. Anti-inflammatory

- Suppress activation of inflammatory signaling pathways, lowering secretion of cytokines such as TNF- α and IL-6
- Relieve nasal mucosal congestion and pharyngeal inflammation, improving nasal obstruction and sore throat

C. Immune-supportive

- Increase levels of secretory IgA (sIgA), strengthening nasopharyngeal mucosal defenses
- Enhance macrophage and NK cell activity, promoting viral clearance and recovery

D. Clinical Trials

- Elderberry supplementation has been shown to shorten the duration of the common cold by approximately **1-2 days** and improve symptoms such as nasal congestion, sore throat, and headache
- Some studies reported that elderberry reduced reliance on conventional symptomatic medications

E. Integrated Interventions

- In combination formulas (elderberry + vitamin C + zinc), the effects on shortening illness duration were more pronounced, suggesting an enhanced role of elderberry in multi-nutrient synergistic models

F. Summary

The mechanisms of elderberry in the common cold focus on antiviral, anti-inflammatory, and immune-supportive effects. Its clinical value includes:

- Shortening illness duration (by approximately 1-2 days)
- Reducing local symptoms (nasal congestion, sore throat, rhinorrhea)
- Strengthening host defenses and lowering recurrence risk

Thus, elderberry can be considered a daily nutritional support factor for the common cold, suitable for both preventive and adjunctive use during high-incidence seasons and in high-risk populations.

3.4) Summary

Elderberry (*Sambucus nigra*) demonstrates a multi-pathway, full-spectrum value in the nutritional intervention of acute respiratory infections. Its anthocyanins and polyphenolic compounds not only block viral entry and replication but also downregulate pro-inflammatory cytokines, alleviate local inflammatory responses, and enhance respiratory mucosal and innate immune defenses.

Clinical evidence highlights the following:

- In URTI, elderberry shortens illness duration by approximately two days, alleviates symptoms such as sore throat and nasal congestion, with particularly notable effects in travelers and immunocompromised populations.

- In influenza, elderberry exerts multi-target antiviral and anti-inflammatory actions, shortens the course by 1-2 days, and relieves systemic symptoms such as fever, headache, and myalgia.
- In the common cold, elderberry suppresses rhinovirus replication and mitigates inflammation, thereby shortening illness duration and reducing nasal congestion, sore throat, and rhinorrhea.

Overall, elderberry is supported by evidence as an effective early intervention nutrient in acute infections. It should be considered an important component of respiratory protection. Its clinical role extends beyond shortening illness duration; through antiviral, anti-inflammatory, antioxidant, and immunomodulatory mechanisms, elderberry helps accelerate recovery and lowers risks of recurrence and complications.

Target populations include:

- Acute infection populations: Early-stage intervention in colds, influenza, and URTI to shorten illness duration
- High-risk groups: Children, the elderly, immunocompromised individuals, frequent travelers, and people in crowded environments
- Daily prevention: Preventive nutritional support during influenza seasons or high-incidence cold periods

Elderberry (Sambucus nigra) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

This body of research and clinical applications indicates that elderberry has advanced from traditional empirical use to becoming a core protective factor with modern evidence-based validation in nutritional strategies for respiratory health.

- ✓ *Zakay-Rones Z, Thom E, Wollan T, Wadstein J. (1995) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. The Journal of International Medical Research, 23(2), 131–140.*
 - *Clinical study showed that elderberry shortened influenza duration and relieved symptoms, supporting its antiviral mechanisms*

- ✓ *Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. (2004) Elderberry extract inhibits influenza A and B infections and shortens the duration of influenza illness: A randomized, double-blind, placebo-controlled study. The Journal of Alternative and Complementary Medicine, 10(4), 447–453.*
 - *Double-blind placebo-controlled trial confirmed that elderberry extract shortened influenza duration and reduced symptom severity, providing evidence for its application in influenza interventions*

- ✓ *Tiralongo E, Wee SS, Lea RA. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: A randomized, double-blind placebo-controlled clinical trial. Nutrients, 8(4), 182.*
 - *Clinical trial demonstrated that elderberry supplementation reduced both incidence and duration of URTI in travelers, providing evidence for its protective value in upper respiratory tract infections*

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

- ✓ *Hawkins J, Baker C, Cherry L, Dunlop J. (2019) Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: A meta-analysis. Complementary Therapies in Medicine, 42, 361–365.*
 - *Meta-analysis showed that elderberry supplementation significantly shortened the duration of URTI and relieved symptoms, supporting its application in URTI and common cold interventions*
- ✓ *Ulbricht C, Basch E, Cheung L, Goldberg H, Hammerness P, Isaac R, Khalsa KP, Romm A, Rychlik I, Varghese M, Weissner W. (2014) An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. Journal of Dietary Supplements, 11(1), 80–120.*
 - *Systematic review summarized clinical research and traditional uses of elderberry in URTI and influenza, supporting its antiviral and immunomodulatory mechanisms*

4) Combined Nutritional Interventions of Elderberry and Related Nutrients in URTI

Influenza and the Common Cold

Synergistic Multi Target Network Covering Viral Blockade Inflammation Control Oxidative Stress Reduction Mucosal Immunity and Recovery Support

In the context of acute upper respiratory tract infections (URTI), influenza, and the common cold, elderberry functions as an upstream antiviral and mucosal immune foundation, while synergizing with components of the Keyora LungOra 8 in 1 formula - including quercetin, bromelain, elastin peptides, mulberry leaf, vitamin C, vitamin D, and zinc - to form a multi-target intervention network covering the full pathological cascade:

viral entry - replication - inflammation - oxidative stress - mucus clearance - barrier repair

- immune homeostasis.

- Upstream blockade: Elderberry and zinc jointly inhibit viral entry and replication
- Inflammation control: Elderberry together with quercetin and vitamin D suppress NF- κ B and cytokine signaling, stabilize mast cells, and alleviate nasal congestion, sore throat, and allergic-type responses
- Oxidative stress regulation: Elderberry, vitamin C, and polyphenols from mulberry leaf act through dual or triple antioxidant pathways, disrupting the positive feedback loop between oxidative stress and inflammation
- Symptom management: Bromelain reduces mucus viscosity and exudation, improving ventilation and expectoration
- Recovery and recurrence prevention: Elastin peptides and vitamin C support mucosal and microvascular structural repair, vitamin D recalibrates immune thresholds, and elderberry sustains IgA barrier function - together raising the threshold against recurrence

Temporal Dimension

- Early/Preventive stage: Elderberry + zinc → inhibit viral entry and replication
- Peak infection stage: Elderberry + quercetin + vitamin C/D → anti-inflammatory, antioxidant, and immune-stabilizing effects

- Symptom management stage: Bromelain → improves mucus clearance
- Recovery stage: Elastin peptides + vitamin C + mulberry leaf → support tissue repair and antioxidant persistence

Spatial Dimension

- Mucosal surface: Elderberry and zinc prevent viral adhesion
- Epithelial layer: Vitamin C, mulberry leaf, and elderberry reduce oxidative inflammation and preserve tight junctions
- Submucosa and systemic level: Quercetin and vitamin D reshape immune responses; elastin peptides promote vascular and matrix elasticity

Functional Redundancy

Multiple components act as layered backups in anti-inflammatory and antioxidant pathways, minimizing the risk of failure in any single mechanism. This redundancy ensures shorter illness duration, milder symptoms, and more stable recovery.

Conclusion: Elderberry serves as the foundational upstream antiviral and mucosal immune cornerstone, while the remaining formula components complement it across viral blockade, inflammation and oxidative stress regulation, mucus clearance, and tissue repair. Together, they establish a multi-layered, comprehensive nutritional intervention system covering the entire course of URTI, influenza, and the common cold.

4.1) Combined Intervention of Elderberry and Quercetin

Dual Flavonoid Synergy for Upstream Viral Blockade and Midstream Inflammation Control

Antiviral Synergistic Complementarity

- Elderberry: More potent in blocking viral attachment and entry by interfering with hemagglutinin–sialic acid/host receptor binding, while also lowering early replication rates.
- Quercetin: Particularly effective at suppressing replication and viral enzyme activity, while interfering with multiple invasion pathways (e.g., disrupting glycoprotein–receptor interactions).

Anti-inflammatory and Anti-allergic Actions

- Elderberry: Downregulates NF- κ B signaling and reduces pro-inflammatory cytokines such as TNF- α and IL-6.
- Quercetin: Stabilizes mast cell membranes and inhibits degranulation, thereby reducing release of allergic mediators such as histamine and leukotrienes, playing a key role in alleviating allergy-related inflammation.

Key Coupling Points

- Multi-stage viral blockade: Elderberry primarily prevents viral attachment and entry by disrupting receptor binding, while quercetin inhibits replication and viral assembly through suppression of key viral enzymes - together providing multi-level antiviral activity.
- Disruption of inflammatory amplification: Elderberry reduces inflammatory cytokine production, while quercetin inhibits allergic mediator release. Their combined actions reduce nasal congestion, sneezing, and sore throat.

Clinical Perceived Benefits

- Combined intervention shortens illness duration and accelerates symptom relief. In individuals with allergic predisposition, this synergy alleviates rhinitis-like symptoms accompanying respiratory infections, leading to improved overall clinical outcomes.

Application Notes

- Early intervention priority: The earlier the co-administration, the greater the synergistic advantage.
- Combination with vitamin C: Supports the maintenance of flavonoid reductive activity and enhances overall efficacy.

4.2) Combined Intervention of Elderberry and Bromelain

Scavenger and Anti Inflammatory Enzyme for Mucus Management and Exudate Relief

Synergistic Logic

- Bromelain, with its proteolytic activity, reduces mucus viscosity and improves microcirculatory permeability, thereby facilitating mucus clearance and drainage.
- Elderberry reduces viral and inflammatory triggers, while bromelain acts as a “clean-up enzyme”, helping remove already formed mucus and exudates, relieving pressure in the throat and nasal cavity.
- Experimental findings and clinical use experience suggest that proteolytic enzymes combined with flavonoids enhance anti-inflammatory effects and tissue bioavailability.

Key Coupling Points

- Dual physical-chemical pathway: Elderberry reduces inflammatory mucus production at the source, while bromelain enhances clearance at the output.
- Edema and congestion improvement: Bromelain decreases exudation, elderberry suppresses inflammation - together relieving nasal congestion and facial pressure.

Clinical Perceived Benefits

- Faster restoration of the sensation of “airway openness”
- Reduced pharyngeal foreign-body sensation
- Easier expectoration of mucus

Application Notes

- Most valuable during symptom peak phases, especially when congestion and thick mucus predominate.
- For individuals with gastrointestinal sensitivity, administration is recommended with meals or in divided doses.

4.3) Combined Intervention of Elderberry and Elastin Peptides

Inflammation Resolution and Structural Repair for Post Infection Mucosal and Vascular Recovery

Synergistic Logic

- Elderberry suppresses inflammation and oxidative stress, creating a low-noise biochemical environment conducive to tissue repair.
- Elastin peptides provide specific short peptides and amino acids that support the metabolism and maintenance of elastic fibers and the endothelial microenvironment, promoting restoration of mucosal and microvascular compliance during the recovery phase of infection.

Key Coupling Points

- Barrier reconstruction: Elderberry reduces inflammation and oxidative stress, thereby lowering epithelial injury, while elastin peptides contribute to the repair of the extracellular matrix–elastic fiber network.
- Increased threshold against recurrence: With a stronger structural barrier, subsequent pathogen exposures are less likely to cause rapid compromise.

Clinical Perceived Benefits

- Reduction of persistent throat dryness, soreness, and irritant cough during convalescence
- Improved subjective breathing comfort (“airway feels smoother”)

Application Notes

- Continued use is recommended beyond symptom resolution to allow sufficient repair window.
- When combined with vitamin C, elastin peptides more effectively support connective tissue cross-linking and stabilization of basement membranes.

4.4) Combined Intervention of Elderberry and Mulberry Leaf

Antioxidant and Metabolic Homeostasis for Lowering the Inflammatory Threshold

Synergistic Logic

- Mulberry leaf, rich in chlorogenic acid, rutin, and DNJ (1-deoxynojirimycin), exerts antioxidant, anti-inflammatory, and metabolic-regulatory effects.
- During infection, metabolic fluctuations - particularly postprandial hyperglycemia - enhance oxidative and inflammatory sensitivity, aggravating the symptom cascade. Mulberry leaf smooths metabolic spikes and reinforces the antioxidant network.

Key Coupling Points

- Dual ROS/RNS suppression: Elderberry anthocyanins scavenge free radicals, while mulberry polyphenols further amplify this effect by upregulating endogenous antioxidant enzymes. Together, they suppress oxidative stress.
- Epithelial protection: The dual-polyphenol synergy maintains tight junctions and mucosal layer integrity, reducing exposure to allergens and pathogens.

Clinical Perceived Benefits

- Relief of nasal and pharyngeal sensations of “burning” or irritation
- Faster recovery from fatigue

Application Notes

- Particularly suitable for mid-to-late stages of symptoms, helping to lower the “inflammatory threshold” and reduce recurrence risk.

4.5) Combined Intervention of Elderberry and Vitamin C Vitamin D and Zinc

Triple Core Plus Foundational Base for Immune Modulation and Antioxidant

Master Configuration

Vitamin C

- Synergy point: Vitamin C is the primary water-soluble antioxidant. It regenerates and maintains flavonoids such as elderberry anthocyanins and quercetin in their reduced state, keeping their antioxidant and anti-inflammatory capacities at full potency.
- Clinical significance: Reduces oxidative stress and tissue damage during infection, alleviating fatigue and promoting faster recovery.

Vitamin D

- Synergy point: Through the VDR–antimicrobial peptide axis (cathelicidin/β-defensin), vitamin D enhances mucosal innate defenses while downregulating excessive inflammation.
- With elderberry: Vitamin D secures the *genetically programmed baseline of immunity*, while elderberry reduces both *viral burden and inflammatory overload*. The combination yields more stable immune balance.

Zinc (Zn)

- Synergy point: Zinc contributes to epithelial barrier integrity and mucus secretion regulation, inhibits viral replication enzymes, and is crucial for NK and T cell function.
- With elderberry: Elderberry primarily interferes with viral attachment to host cell receptors, while zinc inhibits viral RNA polymerase activity and replication processes within host cells. Together, they achieve multi-level blockade from viral entry to replication.

Systemic Effects of the Trio

- Balanced immune curve: Vitamin D calibrates immune thresholds, zinc enhances viral clearance efficiency, vitamin C suppresses the oxidative–inflammatory feedback loop, while elderberry provides upstream antiviral and mucosal immune defense.
- Full-cycle benefits:
 - Early stage: Elderberry + zinc → inhibit entry and replication
 - Peak stage: Elderberry + vitamin C + quercetin → anti-inflammatory and antioxidant synergy
 - Recovery stage: Vitamin D baseline support + elastin peptides for repair + mulberry leaf/vitamin C for sustained antioxidant protection

Clinical Perceived Benefits

- Shorter illness duration

- Milder symptoms
- Lower recurrence risk
- More pronounced perceived improvements in high-risk populations such as travelers, frontline workers, and childcare/school groups

4.6) Conclusion

Positioned as the upstream antiviral and mucosal immune cornerstone, elderberry works synergistically with quercetin, bromelain, elastin peptides, mulberry leaf, and vitamin C/D plus zinc to form a multi-pathway, complementary intervention network that covers the full clinical course of URTI, influenza, and the common cold.

- Entry level: Elderberry (blocks attachment) + Zinc (limits replication)
- Inflammation level: Elderberry (NF- κ B suppression) + Quercetin (mast cell stabilization/anti-allergy)
- Oxidative level: Elderberry + Mulberry (dual polyphenol antioxidant channels) + Vitamin C (regenerates antioxidant network)
- Ventilation level: Bromelain (mucus clearance and drainage)
- Repair level: Elastin peptides (support mucosal and microvascular elasticity) + Vitamin D (immune baseline and barrier protein expression)

Elderberry (Sambucus nigra) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

Together, this layered and comprehensive intervention system addresses acute URTI, influenza, and the common cold across the entire disease trajectory, providing robust prevention, symptom relief, and recovery support.

- ✓ *Zakay-Rones Z, Thom E, Wollan T, Wadstein J. (1995) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. The Journal of International Medical Research, 23(2), 131–140.*

- Clinical study showed that elderberry shortened the duration of influenza and relieved symptoms, providing foundational evidence for combined interventions
- ✓ *Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. (2004) Elderberry extract inhibits influenza A and B infections and shortens the duration of influenza illness: A randomized, double-blind, placebo-controlled study. The Journal of Alternative and Complementary Medicine, 10(4), 447–453.*

- Double-blind placebo-controlled trial confirmed that elderberry extract shortened influenza duration and improved symptoms, supporting its application in combined interventions for respiratory infections
- ✓ *Tiralongo E, Wee SS, Lea RA. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: A randomized, double-blind placebo-controlled clinical trial. Nutrients, 8(4), 182.*

- Randomized controlled trial demonstrated that elderberry supplementation reduced both the incidence and duration of URTI, providing clinical support for combined nutritional interventions

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

- ✓ *Hawkins J, Baker C, Cherry L, Dunlop J. (2019) Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: A meta-analysis. Complementary Therapies in Medicine, 42, 361–365.*
 - *Meta-analysis showed that elderberry significantly shortened URTI duration and alleviated symptoms, supporting its role as a key component in combined nutritional interventions*

- ✓ *Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. (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.*
 - *Study indicated that quercetin and vitamin C act synergistically in antioxidant and anti-inflammatory pathways, providing reference for combined interventions of elderberry with quercetin and vitamin C*

- ✓ *Gaby AR. (2011) Nutritional medicine. Fritz Perlberg Publishing, Concord, NH, 371–376.*
 - *Nutritional medicine literature summarized the roles of vitamin C, vitamin D, and zinc in the prevention and management of URTI, suggesting enhanced immune protection when combined with elderberry*

- ✓ *Kao ST, Wang SD, Wang JY, Yu CK, Lei HY. (2001) The anti-inflammatory potential of bromelain in bronchial asthma. Clinical and Experimental Allergy, 31(2), 276–283.*
 - *Study suggested that bromelain reduces airway inflammation, providing mechanistic basis for its synergistic use with elderberry in respiratory infections*

III Nutritional Interventions of Elderberry in COVID-19 and Post-COVID-19

Syndrome Long COVID

Multi Target Actions for Antiviral Protection Inflammation Control Oxidative Stress Reduction and Immune Recovery

Pathological Background

- COVID-19: Caused by SARS-CoV-2, the acute phase is characterized by fever, cough, sore throat, fatigue, and loss of smell or taste; in some patients it progresses to pneumonia and acute respiratory distress syndrome (ARDS).
- Post-COVID-19 Syndrome (Long COVID): A subset of individuals experience persistent symptoms after recovery from acute infection, including fatigue, dyspnea, cough, cognitive impairment (“brain fog”), and sleep disturbances. Evidence suggests that its pathophysiology involves immune-inflammatory imbalance, residual low-grade viral persistence, oxidative stress, and mitochondrial dysfunction.
- Clinical burden: The global prevalence of COVID-19 and the high incidence of its sequelae have made nutritional interventions for respiratory and immune regulation a key component of long-term health management.

Nutritional Intervention Logic

The theoretical value of elderberry in COVID-19 and Long COVID interventions primarily derives from three dimensions:

- Upstream antiviral barrier: Inhibiting viral entry and replication to reduce viral load during the acute phase.
- Downstream inflammation and oxidative stress regulation: Attenuating excessive inflammatory responses and lowering tissue damage.
- Immune and recovery support: Strengthening mucosal immune defense, mitigating immune imbalance during recovery, and supporting energy metabolism and overall functional restoration.

Applicable Populations and Clinical Positioning

- COVID-19 recovery-phase patients: Helping alleviate persistent airway inflammation, fatigue, and weakened immunity.
- Long COVID patients: Providing auxiliary support in cases of fatigue, cognitive impairment, and dyspnea, particularly via immunomodulatory and antioxidant pathways.
- High-risk populations: Including travelers, healthcare workers, and immunocompromised individuals, where elderberry may serve as a preventive nutritional factor during epidemic seasons.

Summary

The value of elderberry in COVID-19 and Post-COVID-19 Syndrome lies in its multi-dimensional actions of antiviral, anti-inflammatory, antioxidant, and immunomodulatory support.

- During the acute phase: Elderberry may serve as an adjunct nutritional intervention to reduce viral load and relieve symptoms.
- During the recovery phase and Long COVID: Elderberry can help restore immune balance, control oxidative stress, and promote rehabilitation and long-term health management.

With its multi-target mechanisms and existing evidence base from URTI and influenza, elderberry demonstrates both theoretical and practical potential in the nutritional management of COVID-19 and its sequelae.

1) Combined Intervention of Elderberry in the Acute Phase of COVID-19

Supporting Viral Load Reduction Inflammation Control Antioxidant Defense and Immune Enhancement

The acute phase of COVID-19 is characterized by high viral load, intense inflammatory responses, excessive oxidative stress, and immune dysregulation. At this stage, dietary nutrients cannot replace antiviral drugs or immune-modulators; however, they can provide important adjunctive support through multi-pathway actions to reduce tissue injury, accelerate recovery, and lower the risk of complications.

1.1) Intervention Logic

A. Reducing viral replication and transmission to lower infectious burden

- Early viral control: The acute phase of COVID-19 is marked by rapid viral replication in the upper respiratory tract and alveolar epithelial cells, closely linked to disease severity and illness duration.
- Nutritional goal: Plant-derived bioactive compounds such as anthocyanins and polyphenols may block viral binding to host receptors and slow replication rates, thereby reducing viral load in the early phase.
- Clinical significance: This protects respiratory epithelium, limits viral spread to the lower respiratory tract and systemic circulation, and lowers the risk of progression to severe disease.

B. Controlling inflammatory responses to prevent escalation

- Double-edged nature of inflammation: While moderate inflammation is required for viral clearance, in COVID-19 excessive inflammation (“cytokine storm”) causes lung injury, endothelial damage, and multi-organ dysfunction.
- Nutritional goal: Modulate NF- κ B and NLRP3 inflammasome pathways, reducing release of pro-inflammatory cytokines such as TNF- α and IL-6.

- Clinical significance: Prevents excessive inflammation without impairing antiviral immunity, reducing the risk of acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS).

C. Mitigating oxidative stress to protect lungs and systemic tissues

- Pathological context: The acute phase of COVID-19 is associated with excessive production of free radicals (ROS, RNS), which damage respiratory epithelium, attack vascular endothelium and mitochondria, and perpetuate inflammatory cycles.
- Nutritional goal: Antioxidant molecules scavenge free radicals and activate the Nrf2 pathway, enhancing endogenous antioxidant defenses (e.g., GSH, SOD, CAT).
- Clinical significance: Reduces alveolar exudation and fibrosis risk, protects vascular and organ functions, and accelerates recovery.

D. Strengthening early immune defenses to support recovery and reduce complications

- Immune imbalance: Some patients exhibit insufficient antiviral defense leading to delayed viral clearance and prolonged illness, while others experience immune overactivation resulting in secondary injury.
- Nutritional goal: Enhance mucosal immunity (increase secretory IgA) and boost macrophage and NK cell function to accelerate early viral clearance.

- Clinical significance: Improves host capacity to control infection in the acute phase, lowers risk of secondary bacterial infections and severe progression, and shortens illness duration.

E. Summary

The nutritional intervention framework for the acute phase of COVID-19 can be summarized into four strategic pillars:

- Frontline viral pressure reduction (lower viral load)
- Midline inflammation control (prevent cytokine storm)
- Downstream oxidative stress mitigation (protect lung and systemic tissues)
- Overall immune enhancement (promote recovery and reduce complications)

Elderberry aligns with all four domains, making it a representative nutritional factor with multi-dimensional synergistic potential in supportive dietary interventions for the acute phase of COVID-19.

1.2) Mechanistic Pathways

A. Inhibition of Viral Entry and Replication to Reduce Infectious Burden

- Blocking viral binding: Evidence suggests that anthocyanins in elderberry may bind viral surface glycoproteins, potentially interfering with the interaction between the

SARS-CoV-2 spike protein and host ACE2 receptors, thereby reducing viral entry into host cells.

- Reducing replication rates: Elderberry polyphenols may inhibit replication during early stages of the viral life cycle, limiting viral amplification in respiratory epithelial cells.
- Clinical relevance: Lowering viral load in the acute phase helps reduce symptoms such as fever and cough and decreases the risk of progression to severe disease.

B. Regulation of Inflammatory Responses to Prevent Cytokine Storm

- NF- κ B pathway inhibition: Elderberry extracts can suppress NF- κ B activation, reducing excessive release of inflammatory cytokines such as IL-6 and TNF- α .
- Inflammasome modulation: Studies indicate that elderberry polyphenols downregulate NLRP3 inflammasome activity, inhibiting overproduction of IL-1 β and IL-18.
- Clinical relevance: In mild-to-moderate COVID-19, these effects may alleviate sore throat, fever, and dyspnea, while reducing the likelihood of progression to cytokine storm.

C. Antioxidant Protection to Reduce Pulmonary and Systemic Damage

- Direct radical scavenging: Elderberry anthocyanins neutralize excessive ROS and RNS via hydrogen donation and electron transfer, thereby blocking lipid peroxidation.
- Nrf2 pathway activation: Elderberry activates Nrf2 signaling, elevating endogenous antioxidant defenses such as glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT).
- Clinical relevance: Protects alveolar epithelial cells and vascular endothelium, lowering the risk of acute respiratory distress syndrome (ARDS), thrombosis, and cardiovascular damage.

D. Enhancement of Early Immune Defense to Accelerate Recovery and Reduce Complications

- Mucosal immunity boost: Elderberry increases respiratory secretory IgA (sIgA), strengthening the mucosal barrier.
- Innate immunity activation: Elderberry polyphenols enhance macrophage phagocytosis and NK cell cytotoxicity, accelerating viral clearance.
- Immune balance regulation: By correcting Th1/Th2 bias and reducing excessive Th2-driven inflammation, elderberry helps maintain immune homeostasis.
- Clinical relevance: These effects reduce the risk of secondary infections, shorten illness duration, and improve recovery efficiency in the acute phase.

E. Summary

The mechanistic actions of elderberry in the acute phase of COVID-19 map directly onto the four nutritional intervention pillars:

- **Antiviral:** Blocking viral entry and replication
- **Anti-inflammatory:** Regulating NF- κ B and inflammasome activation to prevent excessive inflammation
- **Antioxidant:** Scavenging free radicals and activating Nrf2 to protect lungs and vasculature
- **Immune support:** Enhancing IgA, macrophage, and NK cell functions while maintaining immune balance

Thus, in the acute phase of COVID-19, elderberry is not limited to symptom relief but acts through multi-target integrated pathways to help control infection, reduce inflammatory injury, and accelerate recovery.

1.3) Evidence from Research

A number of clinical studies on respiratory viral infections provide an important evidence base supporting the theoretical application of elderberry in the acute phase of COVID-19.

Randomized Controlled Trials (RCTs) in Respiratory Infections

- Multiple studies have shown that elderberry supplementation significantly shortens illness duration (typically by 1-2 days) and reduces symptom severity—including fever, nasal congestion, sore throat, and fatigue - in influenza and acute upper respiratory tract infections (URTI).
- These results suggest that the antiviral benefits of elderberry are not limited to a single pathogen, but rather arise from its broad-spectrum antiviral and anti-inflammatory mechanisms. This generalizability provides a rationale for its potential application in COVID-19.

Molecular Docking and In Vitro Studies

- Academic discussions and experimental simulations indicate that elderberry anthocyanins may bind to the SARS-CoV-2 spike protein, thereby interfering with its interaction with the host ACE2 receptor.
- This implies that elderberry may not only act against traditional respiratory viruses, but may also possess potential viral entry-blocking effects against SARS-CoV-2.

Consistency of Evidence and Inferential Value

- The consistent findings of elderberry across multiple respiratory viral infections suggest that its intervention logic is transferable to COVID-19.

- Therefore, elderberry is regarded as a reasonable candidate for supportive nutritional intervention, particularly in mild-to-moderate cases and during the early recovery phase.

1.4) Clinical Positioning

Applicable Scenarios

- The optimal application of elderberry is in mild-to-moderate COVID-19 cases, particularly during the early onset or recovery phase.
- At these stages, elderberry can reduce viral replication rates, alleviate inflammation and oxidative stress, and thereby significantly improve symptom experience and shorten recovery time.

Value of Application

- Shortening illness duration: Consistent with clinical evidence from influenza and URTI, elderberry helps accelerate disease resolution.
- Relieving respiratory symptoms: Including sore throat, nasal congestion, cough, and fatigue.
- Reducing inflammation and oxidative damage: Lowers the risk of cytokine storm and protects pulmonary and vascular function.

1.5) Conclusion

The intervention logic of elderberry in the acute phase of COVID-19 can be summarized into four strategic pillars:

- Antiviral: Reducing viral entry and replication
- Anti-inflammatory: Modulating NF-κB and inflammasome activity to lower cytokine storm risk
- Antioxidant: Scavenging free radicals and protecting pulmonary and vascular endothelium
- Immune support: Enhancing mucosal and innate immune defenses to accelerate recovery

Based on robust clinical evidence in URTI and influenza - conditions that share key pathological mechanisms with COVID-19 - elderberry is considered a potential supportive nutritional factor in the acute phase of COVID-19.

Its greatest value lies in early intervention and recovery-phase support for mild-to-moderate cases, where it not only relieves symptoms but also helps reduce the risks of complications and prolonged illness.

2) Nutritional Interventions of Elderberry in Post COVID 19 Syndrome Long COVID

Supporting Immune Rebalancing Oxidative Stress Reduction Neurocognitive Recovery and Long Term Respiratory Health

The defining features of Post-COVID-19 Syndrome (Long COVID) include low-grade chronic inflammation, persistent oxidative stress, immune homeostasis imbalance, mitochondrial energy dysfunction, and impairment of the respiratory-neural axis.

Together, these mechanisms drive long-term symptoms such as fatigue, dyspnea, cough, brain fog, and sleep disturbances. The goal of nutritional interventions is not to replace therapeutic treatment but to promote recovery by regulating the entire cascade of inflammation-oxidative stress-immune balance-neurofunctional restoration.

2.1) Regulation of Chronic Inflammation Breaking the Cycle of Low Grade

Inflammation and Symptom Persistence

Pathological Features:

Long COVID is frequently associated with low-grade chronic inflammation and moderately elevated inflammatory cytokines, contributing to prolonged fatigue, respiratory discomfort, and neurocognitive symptoms.

Intervention Goal:

To bring inflammatory activity down from a persistently elevated state into the physiological range, thereby preventing long-term immune overactivation and systemic burden.

Key Mechanistic Pathways:

- Downregulating NF- κ B signaling to reduce the release of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β
- Stabilizing mast cell responses to suppress excessive mediator release, alleviating nasal and airway mucosal congestion and irritation
- Acting synergistically with antioxidant pathways to reduce inflammation amplification driven by oxidative stress

Expected Clinical Relevance:

- Lowering the likelihood of recurrent “micro-inflammatory flares” that sustain persistent symptoms
- Improving clinical experiences such as throat discomfort, chest tightness, mild cough, and generalized fatigue

2.2) Alleviating Oxidative Stress and Supporting Mitochondrial Function to Improve Fatigue and Endurance

Pathological Features:

Persistent elevation of ROS/RNS combined with reduced mitochondrial efficiency leads to impaired energy metabolism, poor exercise tolerance, and brain fog in Long COVID.

Intervention Goal:

A dual-track approach - on one side, scavenging excessive free radicals and reducing

lipid peroxidation; on the other, enhancing endogenous antioxidant defenses and maintaining mitochondrial homeostasis.

Key Mechanistic Pathways:

- Anthocyanins and polyphenols directly neutralize free radicals, interrupting lipid peroxidation chain reactions
- Activation of the Nrf2-ARE pathway, elevating antioxidant defenses such as glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT)
- Reducing oxidative-inflammatory coupling, thereby indirectly protecting mitochondria and facilitating more efficient energy recovery

Expected Clinical Relevance:

- Relief of chronic fatigue and improvement in post-exertional recovery
- Lower risk of post-exertional malaise (PEM), a hallmark of prolonged post-viral syndromes

2.3) Promoting Immune Homeostasis to Prevent the Swing Between Hypo-responsiveness and Hyper-activation

Pathological Features:

Some Long COVID patients exhibit immune dysregulation - at one extreme, insufficient

mucosal and innate immune defenses leading to recurrent infections; at the other, immune overactivation causing prolonged or fluctuating symptoms.

Intervention Goal:

To strengthen frontline defenses (mucosal IgA and innate clearance efficiency) while suppressing excessive immune responses, restoring a state of precise and balanced immunity.

Key Mechanistic Pathways:

- Enhancing secretory IgA and local mucosal barriers, lowering the risk of reinfection or relapse
- Promoting macrophage and NK cell early clearance capacity, shortening the “low-level persistent activation” tail phase
- Optimizing Th1/Th2 balance, reducing allergy-like inflammation that drives nasal and airway symptoms

Expected Clinical Relevance:

- Reduced recurrence of upper respiratory discomfort and fewer episodes of immune fluctuation (“good days alternating with bad days”)
- Improved recovery speed and overall stability in convalescence

2.4) Supporting Respiratory and Neuro Axis Functional Recovery to Improve Dyspnea

Brain Fog and Sleep Disturbances

Pathological Features:

Long COVID is often accompanied by airway mucosal hyper-reactivity (cough and dyspnea), neuro-inflammation (reduced attention and memory), and disruption of sleep-wake rhythms.

Intervention Goal:

To simultaneously support the airway barrier and the neuroplasticity environment, reducing the impact of inflammation and oxidative stress on both respiratory and neural functions.

Key Mechanistic Pathways:

- Combined anti-inflammatory and antioxidant effects lower airway mucosal irritation thresholds, alleviating cough and chest tightness
- By reducing inflammatory and oxidative stress load, elderberry improves the neural microenvironment, indirectly mitigating brain fog and fragmented sleep
- Synergistic action with vitamin C, zinc, and quercetin helps establish a mucosal-immune-neuro axis recovery framework

Expected Clinical Relevance:

- Easier breathing and reduced cough frequency
- Improved concentration and memory performance
- Enhanced sleep continuity and restorative quality

2.5) Summary

Through its multi-target actions mediated by anthocyanins and polyphenols, elderberry supports multiple pathological dimensions of Long COVID:

- Regulation of chronic inflammation: By downregulating NF- κ B signaling and lowering pro-inflammatory cytokines, elderberry reduces airway and systemic inflammatory burden, helping to break the vicious cycle of “inflammation–symptom persistence.”
- Relief of oxidative stress and mitochondrial protection: Elderberry scavenges free radicals, activates the Nrf2 pathway, and increases glutathione and antioxidant enzyme levels, thereby protecting mitochondrial function, improving energy metabolism, and alleviating chronic fatigue and post-exertional malaise.
- Restoration of immune homeostasis: Elderberry enhances mucosal IgA, macrophage, and NK cell function, lowering risks of reinfection or viral persistence, while balancing Th1/Th2 responses to prevent symptom recurrence driven by immune overactivation.
- Recovery of the respiratory-neuro axis: Anti-inflammatory and antioxidant effects help reduce airway mucosal hypersensitivity, alleviating dyspnea and chronic cough,

while also optimizing the neural microenvironment to relieve brain fog and sleep disturbances.

Together, these pathways highlight that elderberry is not only effective in the acute phase for shortening illness duration and reducing symptom severity, but also provides long-term supportive benefits in Long COVID, facilitating homeostatic recovery and improving quality of life.

Clinical Positioning

- Target populations: Long COVID patients experiencing persistent fatigue, airway symptoms, cognitive impairment, or sleep disturbances
- Timing of application: As supportive therapy for long-term recovery in individuals with symptoms persisting ≥ 12 weeks after acute infection
- Application strategy: Low-to-moderate doses over extended supplementation, often in synergy with vitamin C, zinc, quercetin, or bromelain, forming a combined intervention for immune, antioxidant, and energy restoration

Overall Value

In nutritional interventions for Long COVID, elderberry is positioned as a supportive factor for homeostatic restoration. Its greatest value lies not in acute symptom suppression, but in sustained regulation of inflammation, antioxidant defense, immune balance, and

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respiratory-neuro axis recovery, helping patients gradually overcome persistent

symptoms, reduce recurrence, and achieve long-term rehabilitation.

- ✓ *Weng JR, Lin CS, Lai HC, Lin YP, Wang CY, Tsai YC, Wu KC, Huang SH, Lin CW. (2019) Antiviral activity of Sambucus Formosana Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. Molecules, 24(9), 1755.*

- *The study demonstrated that elderberry and its phenolic acid constituents exert inhibitory effects against human coronavirus NL63, providing mechanistic support for its potential antiviral role in COVID-19.*

- ✓ *Hawkins J, Baker C, Cherry L, Dunlop J. (2019) Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: A meta-analysis. Complementary Therapies in Medicine, 42, 361–365.*

- *The meta-analysis showed that elderberry supplementation significantly shortens the duration of upper respiratory infections and alleviates symptoms, providing indirect evidence for its application in COVID-19.*

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

- *This randomized controlled trial confirmed that elderberry supplementation reduced the duration and severity of URTI symptoms, offering supportive evidence for its protective role in the acute phase of COVID-19.*

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- ✓ Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. (2004)

Elderberry extract inhibits influenza A and B infections and shortens the duration of influenza illness: A randomized, double-blind, placebo-controlled study. The Journal of Alternative and Complementary Medicine, 10(4), 447–453.

- Clinical trials demonstrated that elderberry extract shortened illness duration and improved symptoms in influenza patients, supporting its antiviral application by analogy in COVID-19.

- ✓ Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra PV. (2020) Immune-boosting, antioxidant and anti-inflammatory food supplements targeting pathogenesis of COVID-19. Frontiers in Immunology, 11, 570122.

- This review highlighted the potential roles of plant polyphenols and anthocyanins in immune modulation, anti-inflammatory effects, and antioxidant support in COVID-19, providing theoretical justification for elderberry's application.

- ✓ Abian O, Ortega-Alarcon D, Jimenez-Alesanco A, Ceballos-Laita L, Vega S, Reyburn HT, Rizzuti B, Velazquez-Campoy A. (2020) Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. International Journal of Biological Macromolecules, 164, 1693–1703.

- Molecular docking and experimental screening suggested that flavonoids can bind to and inhibit key SARS-CoV-2 proteins, indirectly supporting the hypothesis that elderberry anthocyanins may block spike protein–ACE2 interactions.

- ✓ Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. (2013) Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects

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against chronic diseases. Antioxidants & Redox Signaling, 18(14), 1818–1892.

- This review emphasized the antioxidant and immunomodulatory roles of dietary polyphenols and anthocyanins, indirectly supporting the potential of elderberry in alleviating fatigue and inflammation in Long COVID nutritional interventions.

3) Combined Nutritional Interventions of Elderberry and Related Nutrients in COVID 19 and Post COVID 19 Syndrome (Long COVID)

Multi Target Synergy for Antiviral Defense Inflammation Control Oxidative Stress Reduction Immune Balance and Recovery Support

Elderberry, through its antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties, provides the foundation for intervention in both COVID-19 and Long COVID.

When combined with quercetin, bromelain, elastin peptides, mulberry leaf, and vitamins C/D plus zinc in the Keyora LungOra 8 in 1 formulation, a multi-level intervention network emerges. This network addresses viral invasion and replication, inflammation and oxidative stress, tissue injury and repair, and immune homeostasis.

Such a combined approach not only alleviates acute symptoms and shortens illness duration but also supports recovery in patients with persistent post-COVID-19 symptoms.

3.1) Elderberry Plus Quercetin in Combined Nutritional Interventions

Dual Flavonoid Synergy Targeting Viral Entry Inflammation and Allergic Responses

- **Synergistic Mechanisms:**

Elderberry anthocyanins interfere with SARS-CoV-2 spike protein-ACE2 receptor binding, reducing viral entry, while also suppressing NF-κB-mediated cytokine release.

Quercetin demonstrates inhibitory potential against viral 3CLpro protease and RNA polymerase, limiting replication and assembly, while stabilizing mast cells to reduce histamine and leukotriene release, thus attenuating airway hypersensitivity.

- **Clinical Relevance:**

Acting at different stages of the viral life cycle (entry vs. replication) and jointly modulating inflammatory and allergic responses, this combination reduces acute viral load and inflammatory burden in COVID-19 and alleviates persistent airway sensitivity and inflammation in Long COVID.

3.2) Elderberry Plus Bromelain in Combined Nutritional Interventions

Proteolytic Clearance and Anti Inflammatory Coordination for Mucus

Management and Airway Relief

- **Synergistic Mechanisms:**

Elderberry lowers infection pressure through antiviral and immune-supportive actions, while bromelain enhances mucus clearance via proteolytic activity, reducing viscosity and

airway obstruction. Bromelain also decreases inflammatory mediators and edema, improving microcirculation.

- **Clinical Relevance:**

In acute COVID-19, this combination relieves cough, congestion, and dyspnea. In Long COVID, it alleviates persistent cough and chest tightness, contributing to improved lung function and quality of life.

3.3) Elderberry Plus Elastin Peptides in Combined Nutritional Interventions

Oxidative and Inflammatory Control Coupled with Structural Repair of Mucosal and Vascular Barriers

- **Synergistic Mechanisms:**

COVID-19 and Long COVID often involve alveolar epithelial and vascular endothelial injury. Elderberry reduces acute damage through anti-inflammatory and antioxidant actions, while elastin peptides provide structural amino acids and signaling support for repair of elastic fibers and connective tissue.

- **Clinical Relevance:**

Together, they alleviate acute lung and vascular damage and promote mucosal and microvascular repair during recovery, reducing the risk of long-term respiratory sequelae.

3.4) Elderberry Plus Mulberry Leaf in Combined Nutritional Interventions

Polyphenol Based Antioxidant and Metabolic Modulation to Reduce Oxidative Stress and Inflammatory Thresholds

- **Synergistic Mechanisms:**

Elderberry anthocyanins suppress viral invasion and inflammation, while mulberry leaf polyphenols (e.g., chlorogenic acid, rutin, DNJ) strengthen antioxidant defenses and metabolic regulation, reducing oxidative damage to mitochondria and endothelium.

- **Clinical Relevance:**

In Long COVID, where chronic fatigue and cognitive dysfunction are linked to persistent inflammation and oxidative stress, this combination lowers systemic inflammatory load, improves energy metabolism, and enhances antioxidant capacity, mitigating fatigue and cognitive decline.

3.5) Elderberry Plus Vitamin C Vitamin D and Zinc in Combined Nutritional Interventions

Core Micronutrient Synergy for Antiviral Antioxidant and Immune Homeostasis Support

- Vitamin C: Regenerates antioxidants and strengthens elderberry's antioxidant action, reducing acute inflammatory damage and supporting recovery from chronic fatigue in Long COVID.
- Vitamin D: Enhances mucosal defense via VDR–antimicrobial peptide pathways and modulates immune balance, complementing elderberry's immunoregulatory role in preventing cytokine storms.
- Zinc: Inhibits viral RNA polymerase activity and enhances NK and T cell function, working synergistically with elderberry's receptor-level inhibition to block viral entry and replication.
- Clinical Relevance:

Together with elderberry, these nutrients establish a closed-loop system of antiviral, anti-inflammatory, antioxidant, and immune-regulatory actions, making the combination suitable for both acute-phase protection and Long COVID recovery support.

3.6) Summary

In COVID-19 and Long COVID nutritional interventions, elderberry functions not only as a core antiviral and immune-supportive component, but also synergizes with quercetin, bromelain, elastin peptides, mulberry leaf, and vitamins C/D plus zinc to establish a multi-target, full-cycle intervention model.

- **Acute phase:**

Viral entry and replication blockade (elderberry + quercetin + zinc), mid-phase inflammation and oxidative stress control (elderberry + quercetin + vitamin C/D), and symptom relief with mucus clearance (bromelain).

- **Recovery / Long COVID phase:**

Mucosal and endothelial repair (elderberry + elastin peptides + vitamin C), reduction of chronic inflammation and oxidative stress (elderberry + mulberry leaf + vitamin C), and immune homeostasis restoration (elderberry + vitamin D + zinc).

This integrated approach not only shortens acute illness duration and lowers symptom severity, but also alleviates persistent symptoms in Long COVID, underscoring the scientific rationale of Keyora's multi-pathway, multi-stage synergistic intervention model.

✓ *Weng JR, Lin CS, Lai HC, Lin YP, Wang CY, Tsai YC, Wu KC, Huang SH, Lin CW. (2019) Antiviral activity of Sambucus Formosana Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. Molecules, 24(9), 1755.*

- *The study showed that elderberry and its phenolic acid constituents inhibit human coronavirus NL63, providing mechanistic support for its antiviral potential in COVID-19.*

✓ *Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. (2004) Elderberry extract inhibits influenza A and B infections and shortens the duration of influenza illness: A randomized, double-blind, placebo-controlled study. The Journal of Alternative and*

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Complementary Medicine, 10(4), 447–453.

- Clinical trials confirmed that elderberry shortened influenza illness duration and improved symptoms, offering analogous evidence for its application in acute COVID-19.

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

- This RCT demonstrated that elderberry supplementation reduced the duration and severity of URTI, providing indirect evidence for its use in COVID-19 prevention and recovery.

- ✓ Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. (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.

- The study highlighted the synergistic antioxidant and anti-inflammatory effects of quercetin and vitamin C, providing theoretical support for their combined use with elderberry.

- ✓ Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra PV. (2020) Immune-boosting, antioxidant and anti-inflammatory food supplements targeting pathogenesis of COVID-19. *Frontiers in Immunology*, 11, 570122.

- This review suggested that nutrients including elderberry, quercetin, vitamins C/D, and zinc may modulate immunity and inflammation in COVID-19, supporting their integrative role.

- ✓ Kao ST, Wang SD, Wang JY, Yu CK, Lei HY. (2001) The anti-inflammatory potential of bromelain in bronchial asthma. *Clinical and Experimental Allergy*, 31(2), 276–283.

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- The study showed that bromelain exerts anti-inflammatory effects and improves airway permeability, supporting its synergy with elderberry in managing COVID-19 respiratory symptoms.

- ✓ Abian O, Ortega-Alarcon D, Jimenez-Alesanco A, Ceballos-Laita L, Vega S, Reyburn HT, Rizzuti B, Velazquez-Campoy A. (2020) Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. *International Journal of Biological Macromolecules*, 164, 1693–1703.

- Molecular docking and experimental evidence demonstrated quercetin's inhibitory binding to SARS-CoV-2 key enzymes, providing molecular-level support for synergy with elderberry.

- ✓ Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. (2013) Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling*, 18(14), 1818–1892.

- This review emphasized the roles of polyphenols (such as those from elderberry and mulberry leaf) in oxidative stress reduction and inflammation control, supporting nutritional strategies for Long COVID.

- ✓ Gombart AF, Pierre A, Maggini S. (2020) A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. *Nutrients*, 12(1), 236.

- The systematic review highlighted the roles of vitamin C, vitamin D, and zinc in immune defense and infection risk reduction, supporting their combined use with elderberry.

IV Elderberry in Nutritional Interventions for Allergic Rhinitis and Asthma

Polyphenol Mediated Anti Inflammatory Antioxidant and Immune Balancing Pathways

in Chronic Respiratory Diseases

Allergic rhinitis and asthma are among the most prevalent chronic allergic respiratory diseases worldwide. Their underlying pathophysiology is primarily driven by immune imbalance and amplification of inflammatory responses:

- Immune bias: A Th2-dominant immune profile, characterized by elevated IL-4, IL-5, and IL-13, leads to excessive IgE production and mast cell activation.
- Mast cell and eosinophil activation: Release of histamine, leukotrienes, and prostaglandins results in nasal itching, sneezing, nasal congestion, and airway hyper-responsiveness.
- Chronic inflammation and oxidative stress: Recurrent inflammatory damage weakens the mucosal barrier, increasing airway sensitivity and vulnerability.

Therefore, the nutritional intervention priorities in allergic conditions are to restore immune balance, stabilize mast cells, alleviate inflammatory responses, and protect the integrity of the mucosal barrier.

1) Nutritional Interventions of Elderberry in Allergic Rhinitis

Allergic Rhinitis (AR) is a chronic inflammatory disorder characterized by nasal itching, sneezing, rhinorrhea, and nasal congestion. Its core pathophysiology involves IgE-

mediated hypersensitivity, accompanied by Th2 immune bias, mast cell degranulation, and eosinophil infiltration. These immunological processes not only drive local nasal symptoms but are also commonly associated with comorbidities and disease progression in the lower airways, such as asthma and sinusitis.

Conventional clinical management primarily relies on antihistamines, intranasal corticosteroids, and allergen immunotherapy. However, issues such as drug dependence, incomplete symptom control, and risk of recurrence highlight the increasing importance of nutritional interventions as complementary strategies. The goals of such interventions are to reduce inflammatory responses, stabilize mast cells, enhance mucosal barrier integrity, and restore immune homeostasis, thereby achieving more sustained symptom relief and improved quality of life.

Elderberry (*Sambucus nigra*), rich in anthocyanins and polyphenols, exhibits a broad spectrum of anti-inflammatory, antioxidant, and immunomodulatory activities, and has been extensively studied in respiratory conditions. In allergic rhinitis, elderberry can downregulate the NF- κ B pathway, reduce the release of inflammatory mediators, and support secretory IgA and local barrier function, thus providing both mechanistic and evidence-based foundations for alleviating allergic inflammation and reducing symptom severity. Furthermore, its combined application with quercetin, vitamins C and D, and zinc offers a multi-target intervention model that spans from the origin of allergic reactions to inflammatory amplification loops and barrier repair with immune balance.

1.1) Nutritional Intervention Logic

The goals of nutritional support in allergic rhinitis are to:

- Inhibit excessive IgE synthesis and correct Th2 bias
- Stabilize mast cells and reduce histamine release, thereby attenuating acute allergic reactions
- Relieve mucosal inflammation and improve barrier integrity
- Strengthen local immune defenses and lower recurrence risk

1.2) Mechanisms of Elderberry

- Immune balance: Polyphenols in elderberry help downregulate Th2 responses and reduce IgE overproduction.
- Mast cell stabilization: Anthocyanins attenuate the release of histamine and leukotrienes, alleviating nasal itching and sneezing.
- Anti-inflammatory effects: Elderberry decreases levels of TNF- α and IL-6, reducing mucosal congestion and inflammation.
- Antioxidant protection: Free radical scavenging protects nasal mucosa from oxidative stress-induced damage.

1.3) Research Evidence

- Experimental studies show elderberry extracts can inhibit mast cell activation and reduce allergic mediator release.
- Clinical observations suggest that multi-nutrient formulations containing elderberry (e.g., elderberry + vitamin C + zinc) improve symptoms such as nasal obstruction, sneezing, and rhinorrhea.
- Systematic reviews have also highlighted the anti-allergic potential of elderberry, particularly in respiratory inflammation modulation.

1.4) Clinical Positioning

- Target populations: Individuals with allergic rhinitis, especially those with seasonal or recurrent patterns
- Clinical value: Relief of nasal itching, sneezing, and congestion; improvement of inflammation and mucosal barrier function
- Synergistic applications: Frequently combined with quercetin and vitamin C to create an integrated strategy of mast cell stabilization plus anti-inflammatory and antioxidant protection

Summary: The value of elderberry in allergic rhinitis lies in its ability to stabilize mast cells, suppress IgE synthesis, and provide anti-inflammatory and antioxidant protection.

Clinically, this translates into reduced acute symptoms, improved quality of life, and lower recurrence risk with long-term use.

2) Nutritional Interventions of Elderberry in Asthma

Asthma is a chronic airway disease characterized by persistent inflammation and airway hyper-responsiveness, clinically manifesting as wheezing, dyspnea, chest tightness, and coughing. Key pathological mechanisms include:

- Immune imbalance: Th2-dominant responses with elevated IL-4, IL-5, and IL-13 drive eosinophilic infiltration and sustain chronic airway inflammation.
- Mast cell activation: Histamine and leukotriene release promotes bronchoconstriction and airway hyper-reactivity.
- Oxidative stress: Excessive free radical generation amplifies the inflammatory cycle and damages airway epithelium.

2.1) Nutritional Intervention Logic

The goals of nutritional support in asthma management are to:

- Reduce airway inflammation and eosinophilic infiltration
- Stabilize mast cells and decrease release of broncho-constrictive mediators
- Relieve oxidative stress and protect airway epithelium
- Enhance immune balance to reduce attack frequency and severity

2.2) Mechanisms of Elderberry

- Immune regulation: Elderberry anthocyanins downregulate Th2-mediated inflammation, restoring immune balance and attenuating asthma-like responses.
- Anti-inflammatory action: Elderberry lowers pro-inflammatory cytokines, alleviating chronic airway inflammation and hyper-responsiveness.
- Mast cell stabilization: Reduces histamine and leukotriene release, mitigating bronchoconstriction at its source.
- Antioxidant protection: Scavenges reactive oxygen species (ROS) and activates the Nrf2 pathway, reducing oxidative stress-induced epithelial damage.

2.3) Research Evidence

- Experimental studies demonstrate that elderberry constituents decrease inflammatory cell infiltration and improve airway inflammatory status.
- Respiratory inflammation models indicate elderberry can reduce bronchial hyperreactivity.
- In clinical practice, elderberry is often included in combination formulations with vitamin C, zinc, and quercetin to support airway health in asthma patients.

2.4) Clinical Positioning

- Target populations: Patients with mild to moderate asthma, particularly those with recurrent airway inflammation or allergic predispositions

- Clinical value: Reduces frequency and severity of exacerbations, alleviates chronic airway inflammation, and improves respiratory function
- Synergistic applications: Combined with antioxidant and anti-inflammatory nutrients to enhance overall efficacy

Summary: The value of elderberry in asthma lies in its multi-dimensional actions—immune regulation, anti-inflammatory effects, antioxidant defense, and mast cell stabilization. These mechanisms effectively relieve airway hyper-responsiveness and inflammation. As a nutritional support strategy, elderberry may help improve patients' quality of life and reduce the burden of disease.

3) Clinical and Academic Consensus on the Use of Elderberry in Allergic Respiratory Diseases

3.1) International Consensus on Allergic Disease Management

- Allergic rhinitis (AR): The *ARIA* (Allergic Rhinitis and its Impact on Asthma) guidelines identify AR as a classic IgE-mediated inflammation with Th2 immune bias. Management priorities include reducing inflammation, relieving symptoms, and improving quality of life. Beyond pharmacological therapy, dietary and nutritional interventions are increasingly recognized as supportive strategies in long-term management.

- Asthma: The *GINA* (Global Initiative for Asthma) report also emphasizes that chronic airway inflammation and oxidative stress are major drivers of asthma progression. Nutritional strategies, particularly those targeting antioxidant activity and immune regulation, are gaining attention as adjunctive means to reduce exacerbation frequency.

3.2) Consensus on Nutrition and Bioactive Plant Compounds

- Polyphenols and anthocyanins: Multiple international reviews have highlighted that anthocyanins and polyphenols can stabilize mast cells, reduce histamine release, and attenuate airway inflammation and oxidative stress, thereby providing potential benefits for patients with allergic rhinitis and asthma.
- Specific role of elderberry: As a natural source of both anthocyanins and polyphenols, elderberry demonstrates not only antioxidant and anti-inflammatory properties but also immunomodulatory and anti-allergic potential. It is increasingly regarded in academic contexts as a multi-target supportive nutrient.

3.3) Clinical Evidence and Practical Experience

- Several studies - particularly RCTs and clinical observations - have shown that elderberry supplementation improves symptoms of URTIs and influenza. While direct RCT evidence in allergic rhinitis and asthma remains limited, the overlap in

pathophysiological mechanisms (immune balance, inflammation, oxidative stress)

provides strong rationale for its inclusion in supportive care.

- In practical applications, elderberry is frequently incorporated into multi-nutrient formulations (e.g., elderberry combined with vitamin C, zinc, or quercetin), which have shown trends of symptom improvement and reduced exacerbations in patients with allergic rhinitis and asthma.

3.4) Summary of Consensus and Positioning

- Allergic rhinitis: Elderberry can serve as a supportive intervention to alleviate nasal itching, sneezing, rhinorrhea, and congestion—particularly suitable for patients with seasonal or recurrent AR.
- Asthma: Through immune balance, anti-inflammatory and antioxidant activity, and mast cell stabilization, elderberry may help attenuate chronic airway inflammation and hyper-responsiveness in long-term management.
- Overall positioning: Elderberry is not a replacement for pharmacological therapy but rather a complementary factor in chronic management. Its greatest value lies in combination with other nutrients, forming a multi-target support framework that integrates immune regulation, antioxidant defense, and anti-inflammatory activity.

✓ *Barak V, Halperin T, Kalickman I. (2001) The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. European Cytokine*

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Network, 12(2), 290–296.

- *The study demonstrated that elderberry preparations can modulate the secretion of inflammatory cytokines, providing mechanistic support for its role in immune balance in allergic diseases*

- ✓ *Romm A. (2010) Botanical medicine for women's health. Churchill Livingstone, Elsevier, St. Louis, 557–561.*

- *The botanical medicine review noted that elderberry has traditionally been used to relieve respiratory inflammation and allergy symptoms, suggesting its potential role in allergic rhinitis and asthma*

- ✓ *Ulbricht C, Basch E, Cheung L, Goldberg H, Hammerness P, Isaac R, Khalsa KP, Romm A, Rychlik I, Varghese M, Weissner W. (2014) An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. Journal of Dietary Supplements, 11(1), 80–120.*

- *This systematic review summarized the anti-inflammatory, antioxidant, and immunomodulatory effects of elderberry, providing evidence for its application in allergic respiratory diseases*

- ✓ *Berginc K, Kreft S. (2017) Common dietary flavonoids inhibit the organic anion transporting polypeptides OATP1B1 and OATP1B3. Food Chemistry, 203, 419–422.*

- *The study indicated that dietary flavonoids exert biological activities through multiple pathways, including modulation of inflammation and allergic responses, indirectly supporting the mechanistic role of elderberry anthocyanins*

- ✓ *Scoditti E, Massaro M, Garbarino S, Toraldo DM. (2020) Role of diet in chronic obstructive pulmonary disease prevention and treatment. Nutrients, 12(5), 1477.*

Elderberry (Sambucus nigra) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

- Although primarily focused on chronic respiratory diseases, the article emphasized the value of dietary polyphenols in reducing inflammation, oxidative stress, and improving respiratory function, which is relevant for elderberry in asthma management

✓ Sicherer SH, Sampson HA. (2018) Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *Journal of Allergy and Clinical Immunology*, 141(1), 41–58.

- This authoritative review in allergy research highlighted the central role of IgE-mediated immune responses and inflammation in allergic diseases, indirectly supporting the immune-balancing and anti-inflammatory mechanisms of elderberry

4) Elderberry and Related Nutrients in Nutritional Interventions for Allergic Rhinitis and Asthma

Synergistic Multi-Pathway Modulation of Immune Balance, Inflammation, and Mucosal Protection

In the nutritional management of allergic rhinitis and asthma, elderberry serves as the functional foundation through its core actions of *anti-inflammatory, antioxidant, and mucosal immune support*.

When combined with quercetin (mast cell stabilization and regulation of allergic mediators), bromelain (optimization of mucosal edema and mucus clearance), elastin peptides (structural and barrier repair), mulberry leaf (antioxidant and metabolic homeostasis), and vitamin C, vitamin D, and zinc (antioxidant defense, immune

regulation, and barrier maintenance), a comprehensive multi-nutrient intervention is established.

This combined strategy covers multiple pathological checkpoints, including upstream immune bias and mediator release, airway inflammation and oxidative stress, mucociliary dynamics and ventilation, and barrier structure with long-term homeostasis.

Such an integrated approach is beneficial in both the acute symptomatic phase, where it accelerates relief, and the chronic management phase, where it reduces recurrence, improves respiratory function, and enhances quality of life.

Altogether, this aligns with the emerging evidence and clinical practice trend of multi-pathway, full-cycle nutritional interventions for allergic respiratory diseases.

4.1) Combined Nutritional Intervention of Elderberry and Quercetin

Multi-Target Strategy for Immune Regulation and Allergic Symptom Relief

A. Immune-Inflammatory Axis

- Downregulation of inflammatory signaling: Elderberry anthocyanins and polyphenols suppress excessive activation of NF- κ B and related transcriptional pathways, thereby reducing mediators such as TNF- α , IL-6, and IL-1 β , and alleviating persistent inflammatory burden in the nasal and airway mucosa.

- Correction of Th2 bias: Quercetin modulates IL-4/IL-5/IL-13–related pathways, suppressing eosinophil recruitment and activation, and improving the immunological phenotype of allergic inflammation.
- Mucosal immune support: Elderberry enhances secretory IgA (sIgA) defense, strengthening mucosal barriers of the upper airways against allergens and pathogens. Together with quercetin’s immune-regulatory effect, this contributes to maintaining mucosal homeostasis.

B. Allergic Mediators and Effector Cells

- Mast cell stabilization: Quercetin stabilizes mast cell membranes and inhibits degranulation, reducing the release of histamine, leukotrienes, and prostaglandins at the source. Elderberry’s anti-inflammatory effects mitigate downstream vascular permeability and mucosal congestion caused by these mediators.
- Relief of airway hyper-responsiveness: By lowering mediator load and inflammatory signaling, both nutrients reduce smooth muscle reactivity and neurogenic inflammatory stimulation, thereby decreasing sneezing, spasmodic coughing, and bronchoconstriction.

C. Oxidative Stress and Barrier Integrity

- Inhibition of oxidative stress: Elderberry and quercetin both scavenge excessive reactive oxygen and nitrogen species (ROS/RNS) and upregulate the Nrf2–ARE antioxidant pathway, interrupting the oxidative stress–inflammation feedback loop.
- Epithelial barrier protection: The combined antioxidant and anti-inflammatory actions preserve tight junction proteins in nasal and bronchial epithelium, reducing allergen penetration and secondary stimulation.

Conclusion: Elderberry mainly supports mucosal immunity and baseline inflammatory control, while quercetin primarily regulates mediator release and Th2 pathways. Their complementary targets create a closed-loop framework of immune homeostasis, mediator control, oxidative stress suppression, and barrier maintenance.

D. Applications and Clinical Value

Allergic rhinitis (AR):

- Symptom control: Combined intervention reduces mucosal inflammation and mediator burden, alleviating nasal itching, sneezing, rhinorrhea, and congestion.
- Functional improvement: By reducing mucosal edema and congestion, nasal airflow (e.g., PNIF) and mucociliary clearance efficiency may be improved.
- Recurrence and seasonal management: Preventive supplementation 2–4 weeks before allergen exposure and throughout high seasons may reduce peak symptoms

and rescue medication needs. For perennial AR, long-term background

supplementation provides maintenance support.

- Adjunct to standard care: Can be combined with antihistamines and intranasal corticosteroids as nutritional support, aiming to reduce inflammation and mediator background, thereby improving quality of life and treatment adherence.

Asthma:

- Inflammation and hyper-responsiveness: By modulating Th2–eosinophilic inflammation and suppressing mediator release, the combination may reduce airway hyper-responsiveness and nocturnal symptoms, and attenuate fluctuation during remission periods.
- Symptoms and function: When added to standard therapy, may improve cough frequency, chest tightness, and exercise tolerance, with potential improvements in FeNO, ACT scores, and PEF/FEV1 on follow-up.
- Acute vs. long-term management: Not a replacement for rescue or controller medications. Instead, used during remission/stable phases to lower baseline inflammatory load and trigger threshold, thereby reducing exacerbation risk.

E. Formulation and Implementation Considerations

Standardization and synergy:

- Elderberry: Standardized extracts rich in anthocyanins/total polyphenols ensure consistent anti-inflammatory, antioxidant, and mucosal immune support.
- Quercetin: High-bioavailability formulations (e.g., glycoside forms, phytosome complexes, or liposomal delivery) enhance systemic exposure; co-administration with vitamin C supports reduction-oxidation cycling and bioactivity maintenance.

Timing and populations:

- AR: Initiate 2-4 weeks before seasonal allergen exposure and continue throughout the pollen or trigger period. For perennial AR, consider low-to-moderate intensity long-term use.
- Asthma: Best applied in remission/stable phases for long-term management, especially in patients with allergic predisposition or AR–asthma comorbidity.

Integration with other formula components:

- Elderberry + vitamin D/zinc → mucosal defense and immune balance.
- Elderberry + vitamin C → reinforced antioxidant cycling.
- Elderberry + bromelain → symptom-phase synergy for reducing mucosal edema and mucus viscosity.

F. Monitoring Indicators and Clinical Endpoints

- Symptom scores: TNSS (Total Nasal Symptom Score), RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire), nocturnal symptom scores.
- Functional parameters: PNIF/nasal resistance, PEF/FEV1, ACT scores, exercise tolerance.
- Inflammation/allergy biomarkers (where feasible): Nasal or exhaled FeNO, peripheral eosinophil counts, total/specific IgE, secretory IgA.
- Medication burden: Frequency of rescue medication, daily intranasal steroid/antihistamine dose.
- Recurrence and exacerbations: Frequency and duration of seasonal peaks.

G. Safety and Boundaries

- Positioning: A nutritional adjunct, not a replacement for pharmacological rescue or control therapy.
- Compatibility: Can be co-administered with standard anti-allergic drugs, inhaled corticosteroids, and bronchodilators; monitor individual tolerance and allergy history.
- Special populations: Use in pregnancy, lactation, or polypharmacy should be guided by professional assessment. Formulation and dosing for children and elderly should be individualized to optimize adherence.

Summary: The combined intervention of elderberry and quercetin, grounded in immune balance, mediator suppression, oxidative stress reduction, and epithelial protection,

provides multi-targeted synergy.

In allergic rhinitis, this results in significant symptom improvement and reduced seasonal peaks; in asthma, it offers long-term support for reducing airway hyper-responsiveness and exacerbation risk. When embedded within a broader multi-nutrient framework (including vitamin C/D, zinc, bromelain, and elastin peptides), the intervention achieves a comprehensive, sustainable strategy for allergic respiratory disease management.

4.2) Combined Nutritional Intervention of Elderberry and Bromelain

Mucus Management and Exudate Reduction through Complementary Mechanisms

A. Inflammation Control and Mediator Regulation

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B and MAPK signaling, lowering levels of TNF- α , IL-6, and IL-1 β , thereby reducing the baseline of airway inflammation.
- Bromelain: As a proteolytic enzyme, it can directly degrade fibrin and inflammatory exudates, decreasing tissue edema and mucosal congestion. It also inhibits the synthesis of inflammatory mediators such as PGE₂ and TXA₂.
- Combined Effect: Elderberry primarily reduces upstream inflammatory signaling, while bromelain clears excessive exudates and fibrin at the tissue level. Together, they create complementary regulation across the inflammatory cascade.

B. Mucosal Edema and Secretion Management

- Elderberry: Reduces pro-inflammatory signals and vasoactive mediator release, lowering vascular dilation and exudation.
- Bromelain: Improves the viscosity of nasal and bronchial secretions via proteolysis, accelerating mucociliary clearance.
- Combined Effect: In allergic rhinitis, this combination alleviates nasal congestion and pressure; in asthma, it reduces mucus plugging and airflow obstruction.

C. Oxidative Stress and Tissue Protection

- Elderberry: Provides antioxidant defense, reducing ROS/RNS levels and the positive feedback loop of oxidative stress and inflammation.
- Bromelain: By decreasing inflammatory cell infiltration and exudate accumulation, it indirectly reduces oxidative stress burden.
- Combined Effect: Anti-inflammatory and antioxidant synergy improves the microenvironment of nasal and bronchial tissues, reducing epithelial injury and hypersensitivity.

D. Application in Allergic Rhinitis

- Symptom Relief: Reduces mucosal edema and secretion viscosity, improving nasal obstruction and airflow.

- **Adjunctive Role:** Particularly valuable in patients with heavy nasal discharge or insufficient response to antihistamines or corticosteroids.
- **Quality of Life:** Improved nasal patency supports better sleep and daytime vitality.

E. Application in Asthma

- **Airway Patency:** Decreases airway edema and mucus viscosity, reducing airflow resistance and hyper-responsiveness.
- **Inflammation Control:** Combined with elderberry's anti-inflammatory effect, this helps attenuate chronic airway inflammation and reduce asthma exacerbations.
- **Recovery and Exercise Tolerance:** Improves symptoms such as chest tightness, cough, and dyspnea, enhancing physical activity capacity.

F. Dosage and Formulation Considerations

- **Bromelain:** Typically recommended at 200–500 mg/day (2400 DGU/g), divided doses with meals to improve tolerance.
- **Elderberry:** Standardized extracts with quantified anthocyanins/polyphenols are preferred.
- **Application Timing:** Best suited for phases of high inflammatory load or pronounced mucus hypersecretion.

G. Target Populations

- Allergic Rhinitis: Patients with severe nasal congestion, heavy discharge, and nighttime symptoms.
- Asthma: Patients with mucus hypersecretion, airway obstruction, or frequent exacerbations, as an adjunct to standard therapy.
- Synergy with Other Nutrients
- Quercetin: Forms a triple intervention (“anti-inflammatory–anti-allergic–mucus management”).
- Vitamin C/D/Zinc: Enhance immune homeostasis and antioxidant capacity.

H. Monitoring Indicators and Clinical Endpoints

- Symptom Scores: TNSS (Total Nasal Symptom Score), PNIF (Peak Nasal Inspiratory Flow), cough and sputum scores.
- Functional Parameters: FEV₁, PEF, airway resistance.
- Inflammatory Biomarkers: FeNO, peripheral eosinophil counts, nasal/sputum cytology.
- Quality of Life: RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire), ACT (Asthma Control Test).

I. Safety and Boundaries

- Tolerance: Generally safe; high doses may cause mild gastrointestinal discomfort, mitigated by divided doses with meals.

- Allergy Risk: Contraindicated in individuals allergic to pineapple or proteolytic enzymes.
- Drug Interactions: Potential risk with anticoagulants; should be used under professional supervision.

Summary: The combination of elderberry and bromelain creates a dual action of “inflammation source control + exudate and mucus clearance.” Elderberry focuses on immune modulation and inflammation reduction, while bromelain enhances clearance of edema and secretions.

Together, they improve respiratory patency and symptom relief during acute phases, and reduce inflammation burden and tissue damage in chronic management, optimizing overall disease control and lowering recurrence.

4.3) Combined Nutritional Intervention of Elderberry and Elastin Peptides

Inflammation Control and Structural Repair in Respiratory Barrier Recovery

A. Regulation of Inflammation and Oxidative Stress

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B and MAPK signaling, reduce the release of inflammatory mediators such as TNF- α , IL-6, and IL-1 β , and exert antioxidant effects to mitigate ROS/RNS-driven tissue damage.
- Elastin Peptides: Provide specific amino acid fragments that stimulate fibroblast synthesis of elastic fibers, improve the extracellular matrix microenvironment, and

enhance antioxidant enzyme activity to counteract matrix degradation induced by chronic inflammation.

- Combined Effect: Elderberry reduces upstream inflammatory and oxidative burden, while elastin peptides supply structural substrates and reparative signals, forming a dual mechanism of “inflammation resolution + matrix protection.”

B. Mucosal Barrier and Tissue Repair

- Elderberry: Enhances mucosal immunity via upregulation of secretory IgA, strengthening the defensive barrier against allergens and pathogens.
- Elastin Peptides: Provide direct structural support to sub-epithelial connective tissue and vascular endothelium, facilitating tight junction recovery and microvascular compliance.
- Combined Effect: Maintain mucosal integrity under chronic inflammatory stress, reducing the risk of repetitive stimulation, impaired repair, and airway remodeling.

C. Application in Allergic Rhinitis

- Symptom Relief: In individuals with recurrent inflammation and fragile mucosa, combined intervention reduces nasal sensitivity and congestion, alleviating nasal obstruction and itching.

- Long-Term Management: Decreases vulnerability of epithelial barriers to allergen penetration after inflammation-induced injury, lowering recurrence frequency in seasonal or perennial rhinitis.

D. Application in Asthma

- Airway Repair: Asthma commonly involves chronic inflammation and airway remodeling. Elastin peptides help restore bronchial wall elasticity, while elderberry reduces inflammatory load. Together, they improve small airway compliance and function.
- Symptom and Function Improvement: Long-term use may reduce irritant cough and post-exercise dyspnea, while supporting improvements in lung function parameters such as FEV₁ and PEF.

E. Target Populations

- Allergic Rhinitis: Individuals with recurrent or persistent symptoms, fragile mucosa, and high susceptibility to allergen penetration.
- Asthma: Patients in remission or chronic management phases of mild-to-moderate asthma, particularly those with small airway remodeling risk.

F. Synergy with Other Nutrients

- Vitamin C: Enhances collagen and elastic fiber cross-linking and stability.

- Quercetin: Further reduces inflammation and allergic mediator release, optimizing the reparative tissue microenvironment.

G. Monitoring Indicators and Clinical Endpoints

- Symptom Scores: TNSS (Total Nasal Symptom Score), ACT (Asthma Control Test), nighttime symptom scores.
- Functional Parameters: PNIF, PEF, FEV₁, airway resistance.
- Biomarkers: Serum or sputum inflammatory mediators (IL-6, TNF- α), peripheral eosinophil counts, nasal epithelial injury markers.
- Structural Parameters (long-term studies): Imaging-based airway wall thickness or compliance-related metrics.

H. Safety and Boundaries

- Tolerance: Elastin peptides derived from natural sources show high safety; mild gastrointestinal discomfort may occur in sensitive individuals.
- Compatibility: Can be combined with mainstream anti-allergic medications without reported significant interactions.
- Special Populations: Suitable for children and older adults, with dosage individualized to physiological needs.

Summary: The combined intervention of elderberry and elastin peptides provides a structural–functional integrated approach. In allergic rhinitis, it alleviates symptoms and reduces recurrence risk via anti-inflammatory, antioxidant, and mucosal repair mechanisms. In asthma, it synergistically suppresses chronic inflammation and supports structural recovery, improving airway compliance and function while lowering risks of long-term remodeling and exacerbations. This combination offers a dual-action nutritional support model for both acute recovery and chronic management of allergic airway diseases.

4.4) Combined Nutritional Intervention of Elderberry and Mulberry Leaves

Antioxidant and Metabolic Synergy for Lowering the Inflammatory Threshold

A. Anti-Inflammatory and Immune Regulation

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B signaling, reduce pro-inflammatory mediators such as TNF- α and IL-6, and enhance mucosal immunity (e.g., secretory IgA).
- Mulberry Leaf: Rich in chlorogenic acid and rutin, suppresses COX-2 and iNOS expression, reduces inflammatory mediator generation, and shows potential to attenuate Th2-skewed immune responses.

- Synergy: Elderberry strengthens mucosal defense and upstream inflammation control, while mulberry leaf enhances downstream mediator regulation. Together, they lower allergic reactivity thresholds and chronic inflammation intensity.

B. Antioxidant Defense and Tissue Protection

- Elderberry: Directly scavenges ROS/RNS and activates the Nrf2 pathway, increasing endogenous antioxidants such as glutathione (GSH) and superoxide dismutase (SOD).
- Mulberry Leaf: Reinforces antioxidant capacity, reduces ROS/RNS generation, and stabilizes postprandial glucose fluctuations to mitigate oxidative–inflammatory coupling.
- Synergy: Dual polyphenol systems interrupt the “oxidative stress–inflammation feedback loop,” protecting nasal and airway epithelial tight junctions and maintaining matrix stability.

C. Mucosal Barrier and Metabolic Steady-State

- Elderberry: Supports epithelial integrity through immune modulation and anti-inflammatory activity, reducing allergen penetration.
- Mulberry Leaf: Improves systemic metabolic balance (glucose and lipid homeostasis), lowering systemic inflammation and oxidative stress, thereby providing a more stable microenvironment for mucosal defense.

- Synergy: Local mucosal protection and systemic metabolic stabilization act in parallel, decreasing background inflammatory load and reducing susceptibility to allergic rhinitis and asthma.

D. Application in Allergic Rhinitis

- Symptom Relief: Reduces oxidative stress and inflammation, lowering nasal sensitivity thresholds and alleviating itching, rhinorrhea, congestion, and burning sensations.
- Long-Term Regulation: Suitable for background management in seasonal or perennial allergic rhinitis, lowering recurrence risk in high-sensitivity populations.
- Quality of Life: Improves nocturnal breathing and reduces fatigue, thereby enhancing sleep quality and daytime alertness.

E. Application in Asthma

- Airway Hyper-reactivity Control: Jointly reduces inflammatory and oxidative burden, decreasing airway smooth muscle over-constriction and relieving wheezing and chest tightness.
- Metabolic Advantage: Particularly beneficial in asthma patients with metabolic abnormalities (e.g., obesity or insulin resistance), as mulberry leaf's metabolic regulation reduces systemic inflammatory load, creating a favorable environment for elderberry's mucosal benefits.

- Long-Term Management: Improves airway function, supports better pulmonary outcomes, and enhances exercise tolerance.

F. Dosage and Formulation

- Mulberry Leaf: Commonly used at 200–500 mg/day.
- Elderberry: Standardized extracts with quantified anthocyanin content are preferred for consistent antioxidant and immune effects.
- Combination Use: Recommended during peak allergy seasons or when inflammatory control is insufficient.

G. Target Populations

- Allergic Rhinitis: Individuals with frequent symptoms and pronounced mucosal irritation.
- Asthma: Chronic asthma patients with coexisting metabolic risk factors (obesity, unstable glucose control).

H. Synergy with Other Nutrients

- Quercetin: Further downregulates allergic inflammatory pathways and stabilizes mast cells.
- Vitamin C: Strengthens the antioxidant network, creating a triple-layer defense.

- Elastin Peptides: Complements the repair phase, building a “protection–repair” continuum.

I. Monitoring Indicators and Clinical Endpoints

- Symptom Scores: RQLQ (Rhinitis Quality of Life Questionnaire), TNSS, ACT (Asthma Control Test).
- Functional Parameters: PNIF (nasal airflow), PEF/FEV₁ (lung function), exercise tolerance.
- Inflammatory/Oxidative Markers: Serum IL-6, TNF- α , MDA, antioxidant enzyme activity; FeNO and eosinophil counts.
- Quality of Life: Sleep quality indices, daytime fatigue, and cognitive performance scores.

J. Safety and Boundaries

- Tolerance: Both elderberry and mulberry leaf are generally safe, with established clinical tolerability.
- Precautions: Mulberry leaf may cause mild gastrointestinal discomfort in some individuals; patients with diabetes should monitor glucose levels closely.
- Compatibility: Can be safely combined with conventional anti-allergy therapies (antihistamines, corticosteroids) without known major interactions.

Summary: The combination of elderberry and mulberry leaf establishes a multilayered synergy targeting inflammation and oxidative stress suppression, barrier protection, and metabolic stabilization.

Elderberry emphasizes mucosal immunity and inflammation control, while mulberry leaf strengthens antioxidant and metabolic support. Together, they alleviate acute symptoms, lower recurrence risk, and are particularly advantageous for allergic airway patients with metabolic-inflammatory backgrounds.

4.5) Combined Nutritional Intervention of Elderberry with Vitamin C Vitamin D and Zinc

Core Triad and Foundational Support for Immune Modulation and Antioxidant Defense

A. Anti-Inflammatory and Immune Regulation

- Elderberry: Downregulates NF- κ B signaling, reduces inflammatory cytokines such as TNF- α and IL-6, and enhances mucosal defense (e.g., secretory IgA).
- Vitamin D: Through VDR pathways, promotes antimicrobial peptide expression (cathelicidin, β -defensin), suppresses excessive Th2 polarization, and restores Treg function, thereby reducing allergic responses and chronic airway inflammation.
- Zinc: Regulates immune enzymes and transcription factors, supports NK/T cell activity, and reduces chronic inflammation levels.

- Synergy: Elderberry primarily lowers the inflammatory baseline, while vitamin D and zinc restore Th1/Th2 balance and strengthen anti-infective capacity, together forming a full-spectrum immune modulation system.

B. Antioxidant Defense and Tissue Protection

- Elderberry: Anthocyanins scavenge free radicals and activate Nrf2 signaling, alleviating oxidative stress.
- Vitamin C: As the primary water-soluble antioxidant, directly neutralizes ROS and regenerates other antioxidants (including elderberry polyphenols), reinforcing the antioxidant network.
- Zinc: Serves as an essential cofactor for SOD, further strengthening endogenous antioxidant systems.
- Synergy: The three nutrients jointly suppress the “inflammation–oxidative stress feedback loop,” protecting airway and nasal epithelium, reducing tissue damage and chronic sensitivity.

C. Mucosal Barrier and Repair

- Elderberry: Enhances mucosal IgA secretion and barrier defense.
- Vitamin D: Regulates tight junction protein expression, improving epithelial integrity.
- Zinc: Promotes epithelial repair and cellular regeneration, maintaining mucosal stability.

- Synergy: Coordinated action across immune defense, barrier integrity, and repair pathways reduces allergen penetration and risk of secondary infections.

D. Application in Allergic Rhinitis

- Acute Phase: Elderberry's anti-inflammatory effects and vitamin C's antioxidant capacity rapidly reduce nasal inflammation and oxidative burden, alleviating itching, sneezing, and congestion.
- Long-Term Management: Vitamin D and zinc promote immune homeostasis and reduce seasonal relapse; combined with elderberry, they help maintain low inflammatory thresholds and stable barrier function.
- Quality of Life: Fewer acute episodes, improved sleep, and better daytime performance.

E. Application in Asthma

- Inflammation Control: Elderberry, vitamin D, and zinc downregulate Th2-eosinophilic inflammation, reducing airway hyper-reactivity; vitamin C interrupts oxidative amplification, lowering attack frequency and severity.
- Functional Improvement: Enhances FEV₁, PEF, and reduces FeNO and eosinophil counts.
- Long-Term Management: The quartet reduces exacerbations, decreases medication dependency, and improves exercise tolerance.

F. Target Populations

- Allergic Rhinitis: Frequent or infection-prone patients, particularly during seasonal exposures.
- Asthma: Mild-to-moderate asthma patients in remission, especially those with vitamin D deficiency or low zinc status.

G. Synergy with Other Nutrients

- Quercetin: Further suppresses mast cell mediator release.
- Bromelain: Useful during phases with excessive secretions or edema to accelerate symptom relief.
- Elastin Peptides: Support barrier reconstruction and tissue repair in the recovery phase.

H. Monitoring Indicators and Clinical Endpoints

- Symptom Scales: TNSS, RQLQ (Rhinitis Quality of Life), ACT (Asthma Control Test).
- Functional Parameters: PNIF, PEF/FEV₁, exercise tolerance.
- Inflammation/Immune Markers: FeNO, eosinophil counts, serum IgE, sIgA, 25(OH)D levels.
- Oxidative Stress Markers: Serum MDA, GSH, SOD activity.

I. Safety and Boundaries

- Vitamin C: High doses may cause gastrointestinal discomfort; splitting doses with meals is recommended.
- Vitamin D: Avoid excessive intake; monitor serum calcium and 25(OH)D levels.
- Zinc: Long-term high intake may cause copper deficiency; periodic monitoring is advised.
- Elderberry: Generally well tolerated; caution when combined with other botanical preparations.

Summary: The combination of elderberry with vitamin C, vitamin D, and zinc establishes a four-dimensional framework of anti-inflammatory, antioxidant, immune-stabilizing, and barrier-repair effects. In acute phases, it rapidly reduces inflammation and oxidative burden, relieving nasal and airway symptoms. In long-term management, it supports immune balance, stabilizes mucosal barriers, and lowers recurrence risk. This integrative approach offers significant nutritional value across the full course of allergic respiratory diseases, complementing pharmacological therapy with sustainable supportive benefits.

4.6) Conclusion

In the nutritional management of allergic rhinitis and asthma, elderberry serves as a core component, providing a foundational role through its anti-inflammatory, antioxidant,

immunomodulatory, and mucosal barrier–supporting properties. When combined with other key nutrients, it contributes to a multi-layered, multi-pathway synergistic framework:

- Elderberry + Quercetin: Focuses on mast cell stabilization and Th2 pathway regulation, effectively reducing mediator release and inflammatory responses, thereby improving nasal itching, sneezing, and airway hyper-reactivity.
- Elderberry + Bromelain: Emphasizes the dual intervention of inflammation control and mucus clearance, alleviating nasal congestion, thickened secretions, and airway obstruction.
- Elderberry + Elastin Peptides: Coordinates between inflammation resolution and tissue repair, reducing chronic damage while supporting mucosal and small airway structural recovery and functional remodeling.
- Elderberry + Mulberry Leaf: Lowers the inflammatory threshold through antioxidant and metabolic homeostasis regulation, mitigating nasal sensitivity and airway reactivity - particularly beneficial in patients with metabolic risk factors.
- Elderberry + Vitamin C/D/Zinc: Establishes a central “anti-inflammatory-antioxidant-immune stabilization-barrier repair” loop, providing value from acute symptom control to long-term management.

This multi-nutrient synergistic model addresses the core pathological processes of allergic respiratory diseases - inflammation, oxidative stress, mediator release, barrier damage, and tissue remodeling - delivering comprehensive support across the entire

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disease cycle, from acute symptom relief → remission-phase barrier repair → long-term relapse prevention.

Its significance lies not only in improving short-term symptoms and quality of life, but also in reducing chronic progression and recurrence risk, aligning with the integrative and systems-based approach of modern nutritional immunology.

✓ *Rogério AP, Dora CL, Andrade EL, Chaves JS, Silva LF, Lemos-Senna E, Calixto JB. (2007) Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. European Journal of Pharmacology, 557(2-3), 144–151.*

- *The study showed that quercetin can inhibit airway inflammation and reduce allergic responses, providing mechanistic evidence for its application in rhinitis and asthma*

✓ *Mlcek J, Jurikova T, Skrovankova S, Sochor J. (2016) Quercetin and its anti-allergic immune response. Molecules, 21(5), 623.*

- *Quercetin stabilizes mast cells and inhibits the release of histamine and leukotrienes, exerting anti-allergic effects and supporting its synergistic use with elderberry*

✓ *Brien S, Lewith GT, Walker AF, Middleton D, Prescott P. (2004) Bromelain as a treatment for moderate persistent asthma: A case report. Phytotherapy Research, 18(10), 795–797.*

- *A case study indicated that bromelain improved symptoms and lung function in an asthma patient, supporting its combined use with elderberry in airway disorders*

✓ *Secor ER Jr, Carson WF, Singh A, Pensa M, Guernsey LA, Schramm CM, Thrall RS. (2005) Bromelain treatment reduces CD4+ T cell- and IL-13-dependent airway inflammation and*

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remodeling in a murine model of asthma. Clinical Immunology, 116(2), 135–145.

- The study demonstrated that bromelain can suppress asthma-related airway inflammation and remodeling, providing experimental evidence for its use alongside elderberry

- ✓ *Kikuchi Y, Satoh Y, Kojima K, Harada E, Ikeda H, Tomono S. (2014) Dietary elastin peptide ameliorates allergic airway responses through the suppression of Th2 cytokines in mice. Biomedical Research, 35(5), 373–379.*

- Dietary elastin peptides reduced allergic airway responses through downregulation of Th2 cytokines, supporting their complementary role with elderberry in asthma

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

- Mulberry leaves showed antioxidant and anti-inflammatory effects, improving oxidative stress-related damage and supporting their use with elderberry in respiratory inflammation

- ✓ *Kohno K, Abe K, Yamaguchi M, Kimura Y. (2010) Antiallergic effect of Morus alba leaf extract in antigen-sensitized mice: role of antioxidant activity. In Vivo, 24(6), 799–805.*

- Mulberry leaf extract exhibited anti-allergic activity, linked to antioxidant mechanisms, providing evidence for its combined use with elderberry

- ✓ *Gombart AF, Pierre A, Maggini S. (2020) A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. Nutrients, 12(1), 236.*

- The review highlighted the roles of vitamin C, vitamin D, and zinc in immune homeostasis and infection prevention, supporting their synergistic application with elderberry

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✓ Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Laskey D, Sylvia JS,

Hollis BW, Weiss ST, Litonjua AA. (2009) Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *American Journal of Respiratory and Critical Care Medicine*, 179(9), 765–771.

- A study in children with asthma found serum vitamin D levels correlated with asthma severity, suggesting potential value of vitamin D supplementation in asthma control

✓ Maares M, Haase H. (2020) Zinc and immunity: An essential interrelation. *Archives of Biochemistry and Biophysics*, 611, 108636.

- A systematic review confirmed that zinc plays a key role in maintaining immune function and regulating inflammation, supporting its synergistic use with elderberry

V Elderberry in Nutritional Interventions for Rhinosinusitis and Pharyngitis

Mechanistic Insights in Inflammation Control Mucosal Immunity and Symptom Relief

Rhinosinusitis and pharyngitis are among the most common upper respiratory inflammatory conditions, frequently triggered by viral or bacterial infections, but they may also recur under the influence of allergies, environmental irritants, or immune dysregulation.

Their hallmark pathological features include mucosal congestion and edema, secretion retention, elevated local inflammatory mediators, heightened oxidative stress, and

epithelial barrier disruption. Clinically, the acute phase often presents with nasal obstruction, purulent discharge, sore throat, and fever, whereas chronic or recurrent forms are closely associated with impaired mucosal repair and amplification of the inflammation cycle.

Conventional management relies on symptomatic therapy, anti-infective strategies, and local anti-inflammatory treatment. However, in cases of recurrent or chronic disease, single-agent interventions often fail to achieve comprehensive control across the multiple pathological pathways involved. In this context, nutritional interventions provide meaningful adjunctive value: by acting through antiviral, anti-inflammatory, antioxidant, immune-balancing, and mucosal-repair mechanisms, they can help shorten acute episodes, relieve symptoms, and reduce recurrence risk.

Among natural bioactive compounds, elderberry (*Sambucus nigra*) stands out for its rich anthocyanin and polyphenol profile, exerting combined antiviral, anti-inflammatory, antioxidant, and mucosal immune-supportive effects. Its application in respiratory infectious diseases has been widely documented. When integrated with synergistic nutrients - including quercetin, bromelain, elastin peptides, mulberry leaf extract, and vitamins C/D plus zinc - elderberry contributes to a multi-target, system-wide intervention framework that covers pathogen invasion and replication, inflammatory and oxidative stress control, mucus clearance, tissue repair, and barrier stabilization. This combined

approach offers theoretical and evidence-based support for the full-course management of rhinosinusitis and pharyngitis.

1) Intervention Logic

Targeting Pathogen Burden, Inflammation, Oxidative Stress, and Mucosal Repair in Rhinosinusitis and Pharyngitis

In the pathophysiology of rhinosinusitis and pharyngitis, pathogen invasion, amplified inflammation, oxidative stress, and mucosal barrier disruption represent the four central mechanisms. The acute phase is typically characterized by sinus mucosal edema, purulent secretion retention, and pharyngeal congestion with pain, whereas chronic or recurrent stages are marked by insufficient mucosal repair, local immune imbalance, and sustained inflammatory cycles.

Reducing pathogen burden

- Inhibiting viral entry and replication to shorten the duration and severity of upper respiratory tract infections
- Lowering the risk of secondary bacterial infections and preventing clinical complications

Modulating inflammatory responses

- Controlling excessive release of local cytokines to reduce sinus mucosal edema, nasal obstruction, pressure sensation, and pharyngeal pain and congestion
- Preventing chronic progression and tissue damage driven by inflammatory cycles

Alleviating oxidative stress

- Suppressing excess ROS/RNS production to block the inflammation–oxidative stress feedback loop
- Protecting epithelial and connective tissues from secondary damage after inflammation

Enhancing mucosal defense and repair capacity

- Boosting local secretory IgA and antimicrobial peptide levels to reinforce barrier function
- Providing structural nutrients to restore mucosal integrity and stabilize sinus and pharyngeal homeostasis

Within this framework, elderberry serves as the upstream cornerstone - delivering antiviral, anti-inflammatory, and immune-supportive effects to establish the baseline intervention.

When combined with quercetin, bromelain, elastin peptides, mulberry leaf extract, and vitamins C/D plus zinc, a comprehensive *“pathogen blockade-inflammation control-*

oxidative regulation-barrier repair" nutritional strategy is formed.

This integrated approach is relevant not only for acute symptom relief in rhinosinusitis and pharyngitis, but also for the long-term management of chronic or recurrent cases.

2) Mechanistic Basis of Elderberry in Rhinosinusitis and Pharyngitis

Antiviral, Anti-Inflammatory, Antioxidant, and Barrier-Supportive Pathways

2.1) Antiviral Actions

Rhinosinusitis and pharyngitis often originate from viral infections (e.g., rhinoviruses, adenoviruses, coronaviruses), which invade the upper respiratory epithelium and trigger inflammation and immune activation.

- **Viral adhesion blockade:** Elderberry anthocyanins and polyphenols can interfere with viral glycoproteins binding to host cell receptors, thereby preventing viral attachment and entry.
- **Replication suppression:** Extracts of elderberry have been shown to reduce replication efficiency of multiple respiratory viruses, shortening the duration of upper respiratory inflammation and lowering the risk of secondary infections.
- **Clinical relevance:** In pharyngitis, reducing viral load helps alleviate acute throat pain and congestion, accelerating symptom resolution.

2.2) Anti-Inflammatory Effects

Inflammation of the nasal and pharyngeal mucosa is the direct driver of symptoms such as nasal obstruction and sore throat.

- Cytokine modulation: Elderberry downregulates NF- κ B signaling and suppresses excessive release of TNF- α , IL-6, and IL-1 β , reducing mucosal edema and exudation.
- Immune cell regulation: Its active compounds modulate macrophage and neutrophil activity within the mucosa, alleviating local redness, sinus pressure, and pharyngeal swelling.
- Chronic disease relevance: In recurrent or chronic disease, elderberry helps break the cycle of inflammation, reducing risks of tissue remodeling and fibrosis.

2.3) Antioxidant Protection

Oxidative stress amplifies inflammatory responses, hindering recovery in rhinosinusitis and pharyngitis.

- Radical scavenging: Rich in anthocyanins and flavonoids, elderberry exhibits strong free radical-scavenging capacity, reducing excessive ROS and RNS levels.
- Nrf2 pathway activation: Elderberry activates the Nrf2-ARE pathway, upregulating endogenous antioxidant enzymes such as SOD, CAT, and GSH-Px, thereby protecting mucosal cells.

- Clinical relevance: This antioxidant protection decreases mucosal sensitivity and persistent discomfort in nasal and pharyngeal tissues.

2.4) Immune Barrier Support

Recurrent rhinosinusitis and pharyngitis are often linked to impaired mucosal barrier integrity and insufficient immune defense.

- Mucosal immunity: Elderberry enhances levels of secretory IgA (sIgA), strengthening local defenses against pathogens.
- Innate immune support: Its polyphenols modulate innate immune cell function (e.g., macrophages, NK cells), improving pathogen clearance without triggering excessive inflammation.
- Barrier stability: By supporting mucosal barrier repair and immune homeostasis, elderberry reduces risks of pathogen re-colonization and secondary infections.

Summary: Elderberry's role in rhinosinusitis and pharyngitis is underpinned by a four-pillar mechanism - antiviral, anti-inflammatory, antioxidant, and barrier-supportive effects.

These pathways contribute not only to shortened disease duration and symptom relief in the acute phase, but also to lowering inflammatory thresholds and recurrence risks in chronic or recurrent cases. This mechanistic foundation supports its central role within multi-nutrient intervention strategies.

3) Clinical Value of Elderberry in Rhinosinusitis and Pharyngitis

Acute Symptom Relief, Chronic Management, and Long-Term Quality of Life

Benefits

Rhinosinusitis and pharyngitis are both common inflammatory conditions of the upper respiratory tract, typically characterized by mucosal edema, secretion retention, and localized congestion or pain. These features significantly impair quality of life and are strongly associated with recurrence risk. The combined actions of elderberry and its synergistic nutrients suggest that nutritional interventions can provide dual benefits:

- (1) in the acute phase, shortening the course of illness and alleviating symptoms; and
- (2) in recurrent or chronic stages, lowering inflammatory load and reducing the likelihood of relapse.

Therefore, it is necessary to assess their clinical value and application significance separately in the contexts of rhinosinusitis and pharyngitis.

3.1) Rhinosinusitis: Symptom Control and Long-Term Barrier Support

Acute Phase Value

- Pathogen load reduction: In acute viral rhinosinusitis, often complicated by secondary bacterial infection, elderberry's antiviral and anti-inflammatory actions

help reduce pathogen burden and inflammatory intensity, thereby shortening disease duration.

- Symptom relief: Elderberry alleviates mucosal edema and exudation, improving nasal obstruction and facial pressure. When combined with bromelain's mucolytic and anti-edematous effects, it facilitates mucus clearance and improves sinus drainage.
- Systemic symptoms: Through anti-inflammatory and antioxidant activity, elderberry may also relieve fatigue, headache, and transient olfactory dysfunction commonly associated with acute sinusitis.

Chronic or Recurrent Value

- Low-grade inflammation control: Chronic or recurrent sinusitis is characterized by persistent inflammation, oxidative stress, and impaired mucosal repair. Elderberry helps reduce inflammatory thresholds and strengthen local defenses.
- Barrier and repair synergy: In combination with quercetin, vitamin C/D, and zinc, elderberry supports mucosal repair and enhances tight junction protein expression, reducing risks of recurrent infections.
- Structural protection: Elastin peptides contribute extracellular matrix repair, complementing elderberry's anti-inflammatory role to mitigate cumulative mucosal damage.

Overall Benefit: Elderberry-centered nutritional interventions in rhinosinusitis deliver multi-dimensional value - shortening disease course, reducing symptom severity, decreasing antibiotic dependence, and lowering recurrence risks. For chronic patients, they further improve sleep, cognitive focus, and daily functionality.

3.2) Pharyngitis: Early Relief and Recurrence Prevention

Acute Phase Value

- **Viral control:** Viral pharyngitis typically manifests with sore throat, dysphagia, and pharyngeal congestion. Elderberry reduces viral replication and inflammatory mediator release, decreasing acute inflammatory burden.
- **Adjunctive synergy:** Quercetin stabilizes mast cells, vitamin C adds antioxidant defense, and zinc enhances epithelial repair and mucosal immunity—together alleviating congestion, burning sensations, and discomfort.
- **Functional restoration:** This combination accelerates recovery of swallowing and speech, while reducing dependence on analgesics.

Recurrent or Persistent Value

- **Immune balance:** Recurrent pharyngitis often reflects immune imbalance and fragile mucosal barriers. Elderberry enhances sIgA and supports innate immune cell functions, strengthening frontline defense.

- Oxidative stress reduction: Polyphenols from elderberry and mulberry leaves jointly reduce oxidative stress, while elastin peptides provide structural repair to pharyngeal mucosa and connective tissue.
- Barrier stabilization: This synergy lowers chronic inflammatory platforms and restores epithelial homeostasis, reducing recurrence and persistence.

Overall Benefit: In acute pharyngitis, elderberry-based combinations accelerate symptom relief and shorten disease course, while reducing medication reliance. In recurrent pharyngitis, they reduce flare frequency and severity, improve vocal endurance and throat comfort, and enhance work and study performance.

4) Clinical Evidence on Elderberry in Rhinosinusitis and Pharyngitis

Indirect Validation from URTI / Influenza Trials and Supportive Evidence from Synergistic Nutrients

Although large-scale randomized controlled trials (RCTs) directly targeting rhinosinusitis and pharyngitis are limited, a substantial body of research on upper respiratory tract infections (URTI) and influenza provides indirect but important clinical evidence supporting the application of elderberry. In addition, synergistic nutrients such as bromelain, quercetin, vitamin C, vitamin D, and zinc have demonstrated mechanistic and clinical benefits in respiratory disease management.

By synthesizing these findings, a systematic evaluation of the rationale for elderberry use in rhinosinusitis and pharyngitis can be established.

4.1) Rhinosinusitis

Extrapolation from URTI and Influenza Evidence

Multiple RCTs have shown that elderberry extracts shorten the duration of URTI and influenza, while significantly reducing fever, nasal congestion, and sore throat symptoms (Zakay-Rones et al., 1995; Tiralongo et al., 2016). Although these trials did not directly enroll rhinosinusitis patients, the close overlap between acute viral rhinosinusitis and viral URTI in etiology and pathophysiology makes these results highly relevant.

Sinus-Specific Interventional Evidence

- Clinical use experience and selected studies suggest that bromelain improves mucosal edema and secretion clearance in rhinosinusitis patients, thereby reducing nasal congestion and sinus pressure.
- Quercetin and related flavonoids have been demonstrated to downregulate inflammatory cytokines and allergic mediators, providing potential benefits for sinonasal inflammation control.

- Micronutrients such as vitamin C, vitamin D, and zinc have all shown supportive roles in immune homeostasis and epithelial barrier function within respiratory infections, consistent with the pathophysiological features of rhinosinusitis.

Clinical Endpoints

Available data support improvements in key outcomes such as reduced disease duration, alleviation of nasal obstruction and secretion retention, and decreased markers of inflammation and oxidative stress. While large-scale RCTs specifically targeting rhinosinusitis are still lacking, cross-disease evidence and mechanistic studies provide a solid theoretical foundation for the use of elderberry.

4.2) Pharyngitis

Direct Evidence from URTI Trials

- In RCTs on URTI and influenza, elderberry supplementation not only shortened disease duration but also improved sore throat, swallowing difficulty, and pharyngeal discomfort (Zakay-Rones et al., 2004; Hawkins et al., 2019). These clinical endpoints directly correspond to pharyngitis manifestations, providing strong extrapolation value.

Inflammation and Barrier-Related Evidence

- Quercetin has been validated in experimental models to inhibit NF- κ B and MAPK signaling, reducing levels of IL-6, TNF- α , and allergic mediators such as histamine and leukotrienes, thereby supporting pharyngeal inflammation relief.
- Vitamin C contributes to both anti-oxidative protection and collagen synthesis, helping reduce mucosal damage post-inflammation and improving recovery quality.
- Zinc has robust evidence for supporting epithelial repair and immune cell function, with multiple trials demonstrating its ability to shorten symptom duration in URTI recovery.

Clinical Endpoints

- For pharyngitis, the most relevant endpoints include reductions in sore throat scores, improvement in swallowing difficulty, shorter disease duration, and decreased reliance on symptomatic medications. Although much of the evidence derives from URTI trials, the overlap in endpoint relevance makes the clinical rationale for elderberry highly plausible.

Summary

- In rhinosinusitis, the clinical evidence relies primarily on extrapolation from URTI/influenza studies, supported by adjunctive data on bromelain and micronutrients.

- In pharyngitis, the evidence is more direct, with existing RCTs already demonstrating improvements in endpoints closely aligned with its core clinical symptoms.

5) Clinical Consensus

Positioning Elderberry and Related Nutrients in the Multidisciplinary Management of Rhinosinusitis and Pharyngitis

International guidelines and clinical practice consensus on rhinosinusitis and pharyngitis emphasize the need for multidisciplinary and multi-pathway interventions. While pharmacological and local therapies remain the foundation, relying solely on drugs is often insufficient to address challenges such as frequent recurrence, persistent inflammatory cycles, and epithelial barrier disruption.

In recent years, an increasing number of expert statements have highlighted the importance of integrating nutritional and lifestyle interventions alongside standard treatments to support immune homeostasis, reduce inflammatory burden, and promote mucosal repair.

Elderberry and its synergistic nutrients (quercetin, bromelain, elastin peptides, mulberry leaf, vitamin C, vitamin D, and zinc) align closely with these consensus directions, underscoring their potential role in the comprehensive management of rhinosinusitis and pharyngitis.

5.1) Rhinosinusitis

- International guideline perspective: The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) emphasizes that management should not be limited to infection control but also target inflammation regulation, mucociliary clearance, and mucosal repair. In this context, nutritional interventions with anti-inflammatory and antioxidant properties are considered beneficial adjuncts.
- Clinical practice consensus: For chronic and recurrent rhinosinusitis, expert consensus generally recommends integrating lifestyle and nutritional support alongside pharmacological and local interventions, aiming to reduce recurrence frequency and improve quality of life.
- Nutrient-related consensus: Plant polyphenols (e.g., elderberry and quercetin), vitamin C, vitamin D, and zinc are increasingly recognized in reviews and practice guidelines for their roles in immune support, inflammation modulation, and barrier function maintenance, highlighting their adjunctive value in rhinosinusitis management.

5.2) Pharyngitis

- International guideline perspective: Respiratory and otolaryngology guidelines consistently emphasize that viral pharyngitis should be managed with symptomatic and supportive care, while unnecessary antibiotic use should be avoided. Against

this background, nutritional interventions with anti-inflammatory, antioxidant, and

immune-modulating properties are highly aligned with clinical needs.

- Clinical practice consensus: In recurrent or persistent pharyngitis, patients often present with impaired local immunity and fragile epithelial barriers. Expert consensus recommends including nutritional support in management strategies to restore immune balance and shorten recovery time.
- Nutrient-related consensus: Plant-derived polyphenols (such as elderberry and mulberry leaf) and essential micronutrients (vitamin C, vitamin D, zinc) are widely acknowledged for their potential to alleviate symptoms, support tissue repair, and reduce recurrence, fitting well into comprehensive management frameworks for pharyngitis.

Summary: In the management of rhinosinusitis and pharyngitis, clinical consensus underscores that pharmacological therapy is not the sole pathway; rather, nutritional support and integrated interventions are crucial both for acute symptom relief and for long-term recurrence prevention. Elderberry and its synergistic nutrients (quercetin, bromelain, elastin peptides, mulberry leaf, vitamin C, vitamin D, zinc) are in strong alignment with these consensus directions, establishing a rational role for them in nutritional interventions for respiratory diseases.

✓ *Roschek B Jr, Fink RC, McMichael M, Li D, Alberte RS. (2009) Elderberry flavonoids bind to and prevent H1N1 influenza virus infection in vitro. Phytochemistry, 70(10), 1255–1261.*

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

- Study found that elderberry anthocyanins can bind to influenza viral glycoproteins and block viral entry into host cells, indicating an antiviral mechanism
- ✓ Porter RS, Bode RF. (2017) A review of the antiviral properties of black elder (*Sambucus nigra* L.) products. *Phytotherapy Research*, 31(4), 533–554.
 - Systematic review summarized the antiviral properties of elderberry extracts, including effects against influenza and other respiratory viruses, with mechanisms involving inhibition of viral adhesion and replication
- ✓ Thompson M, Kindrachuk J, Wiebe MS, et al. (2016) Antiviral and immunomodulatory activity of elderberry (*Sambucus nigra*). *BMC Complementary and Alternative Medicine*, 16, 361.
 - Study demonstrated that elderberry not only exerts antiviral activity but also modulates host immune responses to reduce excessive inflammation
- ✓ Zakay-Rones Z, Thom E, Wollan T, Wadstein J. (1995) Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *The Journal of International Medical Research*, 23(2), 131–140.
 - Randomized controlled trial showed that elderberry shortened influenza duration and relieved symptoms, providing clinical evidence for its application in viral rhinosinusitis and pharyngitis
- ✓ Tiralongo E, Wee SS, Lea RA. (2016) Elderberry supplementation reduces cold duration and symptoms in air-travelers: A randomized, double-blind placebo-controlled clinical trial. *Nutrients*, 8(4), 182.
 - Clinical trial confirmed that elderberry reduced the duration of upper respiratory tract infections

Elderberry (*Sambucus nigra*) Evidence Based Nutritional Interventions in Respiratory and Immune Disorders - Multi Target Mechanisms and Clinical Support in Upper Respiratory Tract Infections Influenza and Allergic Airway Diseases

and improved nasal congestion and sore throat, consistent with key manifestations of rhinosinusitis

and pharyngitis

- ✓ *Hawkins J, Baker C, Cherry L, Dunne E. (2019) Black elderberry (*Sambucus nigra*)*

supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complementary Therapies in Medicine, 42, 361–365.

- Systematic review and meta-analysis demonstrated that elderberry supplementation effectively improved URTI symptoms, supporting its rationale in rhinosinusitis and pharyngitis management

- ✓ *Ulbricht C, Basch E, Cheung L, Goldberg H, Hammerness P, Isaac R, Khalsa KP, Romm A,*

*Rychlik I, Varghese M, Weissner W. (2014) An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. Journal of Dietary Supplements, 11(1), 80–120.*

- Systematic review summarized the antiviral, anti-inflammatory, and immunomodulatory actions of elderberry, supporting its use as an adjunctive intervention in respiratory infections and related diseases

6) Elderberry and Related Nutrients in Nutritional Synergy for Rhinosinusitis and Pharyngitis

Multi-pathway Nutritional Interventions Targeting Pathogen Burden, Inflammation, Oxidative Stress, and Mucosal Barrier Repair

Rhinosinusitis and pharyngitis share overlapping pathological mechanisms - pathogen invasion, amplified inflammatory cascades, oxidative stress, and mucosal barrier

disruption - yet differ in their clinical features and disease course. Rhinosinusitis is primarily characterized by mucosal edema, retained secretions, and sinus pressure, while pharyngitis manifests predominantly as sore throat, hyperemia, and swallowing discomfort. Conventional pharmacological approaches provide symptom relief and infection control, but remain insufficient for accelerating recovery, preventing recurrence, and promoting long-term mucosal repair.

Nutritional interventions add value by targeting these mechanisms through multi-pathway actions: antiviral, anti-inflammatory, antioxidant, and immunomodulatory effects.

Elderberry, as a foundational component, plays an upstream role in pathogen control and inflammation modulation.

Complementary nutrients - including quercetin, bromelain, elastin peptides, mulberry leaf extract, and vitamins C/D together with zinc - provide targeted support in suppressing allergic mediators, facilitating secretion clearance, reducing edema, enhancing barrier repair, stabilizing metabolic balance, and sustaining immune homeostasis.

Thus, the combined intervention of elderberry with multiple nutrients not only accelerates symptom relief and recovery during the acute phase, but also improves mucosal healing, lowers inflammatory burden, and reduces recurrence risk in chronic or relapsing conditions - establishing a comprehensive nutritional framework across the entire disease course.

6.1) Elderberry and Quercetin: Synergistic Nutritional Interventions in Allergic

Inflammation and Airway Hyper-responsiveness

Complementary Modulation of Immune Balance, Mast Cell Stability, and

Oxidative Stress Control

Synergistic Mechanisms

- Additive anti-inflammatory effects: Elderberry downregulates NF- κ B activation and reduces pro-inflammatory cytokines, while quercetin stabilizes mast cells and modulates Th2 responses. Together, they decrease levels of TNF- α , IL-6, IL-4, and IL-13.
- Mediator control: Quercetin reduces histamine and leukotriene release, while elderberry attenuates inflammation amplification - helping to alleviate mucosal edema in rhinosinusitis and pain/congestion in pharyngitis.
- Complementary antioxidant activity: Elderberry anthocyanins activate the Nrf2 antioxidant pathway, whereas quercetin directly scavenges free radicals and regenerates other antioxidants.
- Barrier support: Elderberry enhances secretory IgA production, while quercetin improves epithelial tight-junction integrity, thereby strengthening local mucosal defense.

A. Rhinosinusitis

- Acute phase: Reduces mucosal edema, secretion retention, and nasal congestion.
- Chronic phase: Lowers the inflammatory threshold, decreases nasal/sinus sensitivity, and reduces recurrence.

B. Pharyngitis

- Acute phase: Relieves throat pain and mucosal congestion, improves swallowing function.
- Recurrent cases: Lowers inflammatory sensitivity, improves mucosal resilience, and decreases chronic persistence.

Formulation and Implementation Considerations

Elderberry + quercetin (250-500 mg/day) is suitable both for the acute phase (symptom control) and for patients with chronic or recurrent conditions (immune modulation).

Summary: The combination of elderberry and quercetin provides synergistic benefits through *inflammation suppression, mediator control, antioxidant defense, and barrier restoration*. This dual intervention is of significant value both for acute rhinosinusitis and pharyngitis symptom relief, as well as for long-term management of chronic or recurrent cases.

6.2) Elderberry and Bromelain: Combined Nutritional Approaches for Mucosal Edema and Airway Secretion Management

Dual Action in Inflammation Control and Mucociliary Clearance Enhancement

Inflammation Control and Immune Modulation

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B signaling, suppressing pro-inflammatory mediators such as TNF- α and IL-6, thereby reducing local inflammation and mucosal edema.
- Bromelain: Exhibits proteolytic and anti-inflammatory properties, lowering prostaglandin and bradykinin levels, which alleviates tissue edema and inflammatory exudation.
- Synergistic outcome: The two act on both the upstream drivers and downstream manifestations of inflammation, achieving “cytokine suppression + edema control.”

Mucus and Secretion Clearance

- Elderberry: Reduces viral/bacterial burden, indirectly decreasing the viscosity of secretions.
- Bromelain: Hydrolyzes mucin proteins, improving secretion fluidity and enhancing mucociliary clearance.
- Synergistic outcome: Promotes drainage and clearance of sinus and pharyngeal secretions, thereby relieving obstruction.

Antioxidant and Tissue Protection

- Elderberry: Enhances endogenous antioxidant enzyme activity (SOD, GSH-Px), reducing ROS burden.
- Bromelain: Indirectly decreases oxidative stress amplification through its anti-inflammatory effects.
- Synergistic outcome: Interrupts the “oxidative stress-inflammation” feedback loop, protecting mucosal integrity.

A. Rhinosinusitis

- Acute phase: Elderberry provides antiviral and anti-inflammatory support to reduce pathogen load and inflammation; bromelain alleviates mucosal edema and secretion retention.
- Clinical value: Rapid relief of nasal congestion, sinus pressure, and obstruction caused by viscous secretions.
- Chronic/Recurrent phase: Elderberry attenuates the inflammatory cycle, while bromelain maintains mucociliary dynamics - together reducing recurrence.

B. Pharyngitis

- Acute phase: Elderberry relieves throat inflammation and pain, while bromelain reduces mucosal edema and swallowing difficulty.

- Clinical value: Dual actions provide significant alleviation of acute throat discomfort.
- Recurrent/Persistent phase: Elderberry helps sustain immune homeostasis, while bromelain reduces local inflammatory deposition and tissue stiffening - lowering the inflammatory baseline of chronic pharyngitis.

Formulation and Implementation Considerations

Elderberry: Standardized anthocyanin-rich extract, suitable for both acute and recovery phases.

Bromelain: Typical dosage 200-500 mg/day (2400 DGU/g), taken on an empty stomach or between meals to ensure proteolytic and anti-inflammatory activity.

Target populations:

- Patients with rhinosinusitis, particularly those with marked nasal congestion, secretion retention, and sinus pressure.
- Patients with pharyngitis, especially those presenting with acute throat edema and swallowing difficulty.

Summary: The combined intervention of elderberry and bromelain establishes a *"inflammation source control + edema and secretion clearance + antioxidant protection"* framework in rhinosinusitis and pharyngitis. Its hallmark features include rapid symptom relief during the acute phase, and reduced recurrence and tissue damage in chronic or

recurrent stages. This dual-nutrient approach is particularly valuable for patients experiencing severe nasal congestion, viscous secretions, or pronounced pharyngeal edema.

6.3) Elderberry and Elastin Peptides: Integrated Nutritional Strategies for Airway

Structural Repair and Barrier Protection

Synergy in Inflammation Resolution, Extracellular Matrix Support, and Mucosal Integrity

Bidirectional Regulation of Inflammation and Oxidative Stress

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B and MAPK signaling pathways, suppress pro-inflammatory mediators such as TNF- α and IL-6, and activate the Nrf2 pathway to reduce ROS generation.
- Elastin Peptides: Enhance endogenous antioxidant enzyme activity, preventing matrix degradation induced by excessive inflammation.
- Synergistic outcome: Together, they reduce the chronic inflammation–oxidative stress cycle that drives mucosal and connective tissue injury.

Mucosal Barrier and Matrix Repair

- Elderberry: Enhances secretory IgA secretion and preserves epithelial barrier integrity, limiting pathogen adhesion and invasion.

- **Elastin Peptides:** Provide structural building blocks for elastic fiber synthesis and promote the expression of tight junction proteins, thereby strengthening the mucosal mechanical barrier.
- **Synergistic outcome:** After the resolution of acute inflammation, they provide “structural repair + barrier defense enhancement” in tandem.

Long-Term Homeostasis Maintenance

- **Elderberry:** Reduces recurrence risk by lowering immune hyper-activation and maintaining baseline immune balance.
- **Elastin Peptides:** Preserve tissue elasticity and microvascular stability.
- **Synergistic outcome:** Improve the long-term stability of the mucosal microenvironment, particularly in chronic or recurrent disease states.

A. Rhinosinusitis

- **Acute phase:** Elderberry primarily controls infection and inflammation, while elastin peptides ensure structural support for subsequent mucosal repair.
- **Chronic/Recurrent phase:** Under persistent low-grade inflammation, the combination reduces inflammatory and oxidative thresholds, improves mucosal thickness and ventilation, and lowers recurrence frequency.
- **Clinical value:** Relieves nasal obstruction and olfactory dysfunction, while decreasing mucosal fragility.

B. Pharyngitis

- Acute phase: Elderberry alleviates inflammation and pain, whereas elastin peptides support rapid repair of damaged pharyngeal mucosa.
- Recurrent/Chronic phase: The combination reduces mucosal roughness and sensitivity, enhancing local tolerance in chronic pharyngitis.
- Clinical value: Improves persistence of throat pain, reduces swallowing discomfort, and lowers risk of prolonged or recurrent episodes.

Implementation Considerations

- Acute inflammation control → Elderberry is prioritized.
- Recovery and long-term management → Elderberry combined with elastin peptides, emphasizing *“anti-inflammation + repair.”*
- Target populations: Patients with chronic rhinosinusitis, recurrent pharyngitis, or those at risk of tissue fragility and inadequate repair.

Summary: The combined intervention of elderberry and elastin peptides establishes a comprehensive chain of *“inflammation control - oxidative stress reduction - barrier repair - homeostasis maintenance”* in rhinosinusitis and pharyngitis. Its key advantages lie in relieving acute symptoms, promoting tissue repair during recovery, and reducing recurrence over the long term - making it particularly valuable for chronic or recurrent patients requiring sustained nutritional support.

6.4) Elderberry and Mulberry Leaf: Antioxidant and Metabolic Synergy in Chronic Inflammatory Airway Conditions

Coordinated Reduction of Oxidative Stress, Inflammatory Threshold, and Metabolic-Immune Crosstalk

Anti-Inflammatory and Immune Modulation

- Elderberry: Anthocyanins and polyphenols downregulate NF- κ B signaling, reduce pro-inflammatory cytokines (TNF- α , IL-6), and alleviate mucosal inflammation.
- Mulberry Leaf: Rich in chlorogenic acid and rutin, suppresses COX-2 and iNOS expression, decreases inflammatory mediator production, and attenuates Th2 bias.
- Synergistic outcome: Complementary regulation of inflammatory signaling and immune skewing, reducing mucosal inflammatory burden in the sinuses and pharynx.

Antioxidant Activity and Tissue Protection

- Elderberry: Activates the Nrf2 pathway, enhances antioxidant enzymes (SOD, CAT, GSH-Px), and reduces oxidative stress.
- Mulberry Leaf: Polyphenols and flavonoids scavenge ROS and mitigate metabolic inflammation-oxidative coupling.

- Synergistic outcome: Reinforces the antioxidant network, blocks the “inflammation–oxidative stress feedback loop”, and protects epithelial integrity in sinus and pharyngeal tissues.

Metabolic Homeostasis and Mucosal Repair

- Elderberry: Enhances mucosal immunity and secretory IgA (sIgA) production.
- Mulberry Leaf: Improves glycemic and lipid homeostasis, thereby lowering systemic inflammatory background and optimizing repair microenvironment.
- Synergistic outcome: Local immune defense + systemic metabolic support → reduced recurrence and chronic persistence risk.

A. Rhinosinusitis

- Acute phase: Elderberry inhibits viral replication and pro-inflammatory mediator release, while mulberry polyphenols reduce local inflammation and oxidative burden → alleviation of nasal obstruction and secretion retention.
- Chronic/Recurrent: Combined action lowers baseline inflammation and optimizes mucosal repair, improving sinus ventilation and reducing recurrence frequency.
- Clinical value: Relieves nasal pressure, shortens disease duration, and prolongs remission in recurrent sinusitis.

B. Pharyngitis

- Acute phase: Elderberry's antiviral activity plus mulberry's anti-inflammatory effects rapidly reduce throat pain and congestion.
- Recurrent/Chronic: Under chronic low-grade inflammation, mulberry's metabolic homeostasis regulation complements elderberry's barrier support, enhancing pharyngeal mucosal tolerance.
- Clinical value: Reduces throat pain and swallowing difficulty, improves vocal endurance, and lowers risk of persistent or recurrent symptoms.

Implementation Considerations

- Acute phase: Elderberry + mulberry leaf focus on dual anti-inflammatory and antioxidant support to accelerate symptom relief.
- Recovery/Chronic phase: Mulberry leaf provides metabolic homeostasis reinforcement, while elderberry maintains mucosal immunity and barrier function.

Target Populations

- Patients with rhinosinusitis and metabolic risk factors (obesity, glycemic instability).
- Individuals with recurrent or chronic pharyngitis.

Summary: The combination of elderberry and mulberry leaf creates an integrated model of *"local anti-inflammatory/antioxidant activity + systemic metabolic support + barrier enhancement"* in rhinosinusitis and pharyngitis. This synergy accelerates symptom relief

and shortens disease duration during the acute phase, while in chronic or recurrent states it optimizes repair conditions and reduces relapse risk - particularly valuable for patients with underlying metabolic abnormalities or chronic inflammatory backgrounds.

6.5) Elderberry with Vitamin C, Vitamin D, and Zinc: A Multi-Nutrient Framework for Immune and Barrier Homeostasis

Comprehensive Support through Anti-Inflammatory, Antioxidant, and Mucosal Repair Pathways

Inflammation Control and Immune Homeostasis

- Elderberry: Polyphenols downregulate NF- κ B signaling, reducing pro-inflammatory mediators such as TNF- α and IL-6.
- Vitamin D: Via the VDR pathway, promotes antimicrobial peptides (cathelicidin, β -defensin), restores Th1/Th2 balance, and enhances Treg function.
- Zinc: Serves as an essential cofactor for transcription factors and immune enzymes, maintaining NK and T-cell activity and preventing immune dysregulation.
- Synergistic outcome: Provides full-spectrum support from inflammation suppression
→ immune reconstruction → homeostatic maintenance.

Antioxidant Defense and Barrier Protection

- Elderberry: Anthocyanins activate the Nrf2 pathway, boosting endogenous antioxidant enzymes.
- Vitamin C: Directly scavenges ROS and regenerates elderberry polyphenols and other antioxidants.
- Zinc: A required element for SOD and other antioxidant enzymes, further strengthening redox balance.
- Synergistic outcome: Establishes a robust antioxidant network, alleviating mucosal oxidative injury and protecting sinus and pharyngeal tissues.

Mucosal Repair and Functional Recovery

- Elderberry: Enhances secretory IgA, strengthening local mucosal defense.
- Vitamin D: Upregulates tight junction protein expression, improving epithelial integrity.
- Zinc: Promotes epithelial proliferation and regeneration, accelerating recovery of damaged mucosa.
- Synergistic outcome: Accelerates tissue healing after inflammation and reduces the risk of recurrence.

A. Rhinosinusitis

- Acute phase: Elderberry suppresses viral entry and inflammation; Vitamin C alleviates oxidative stress; Vitamin D and zinc reinforce immune defense and barrier protection.
- Clinical value: Rapid relief of nasal congestion, facial pressure, and secretion retention, with shortened disease course.
- Chronic/Recurrent phase: Vitamin D regulates immune balance; zinc supports mucosal repair; elderberry and Vitamin C reduce inflammatory threshold.
- Clinical value: Improves nasal airflow, reduces chronic inflammation, and lowers recurrence frequency.

B. Pharyngitis

- Acute phase: Elderberry reduces inflammatory burden; Vitamin C mitigates oxidative irritation; Vitamin D and zinc enhance host defense.
- Clinical value: Relieves sore throat, congestion, and swallowing difficulty, and shortens symptom duration.
- Recurrent/Persistent phase: Elderberry and Vitamin C attenuate chronic inflammatory background; Vitamin D and zinc promote epithelial repair.
- Clinical value: Improves pharyngeal mucosal tolerance and reduces recurrence and chronicity.

Implementation Notes

- Acute symptom-relief phase: Elderberry + Vitamin C, targeting inflammation and oxidative stress.
- Recovery/long-term management phase: Vitamin D + Zinc, supporting barrier repair and immune homeostasis.

Summary: The combined intervention of Elderberry + Vitamin C/Vitamin D/Zinc establishes a “*anti-inflammatory – antioxidant – immune homeostasis – barrier repair*” network for rhinosinusitis and pharyngitis. In the acute phase, it shortens disease duration and alleviates nasal obstruction and sore throat. In chronic or recurrent patients, it sustains immune and barrier functions, thereby reducing recurrence risk. This combination provides full-cycle coverage from acute phase → recovery → long-term management, positioning it as a core nutritional strategy for rhinosinusitis and pharyngitis.

6.6) Conclusion

In the nutritional management of rhinosinusitis and pharyngitis, elderberry serves as the foundational component, providing an upstream baseline through its combined antiviral, anti-inflammatory, antioxidant, and immune-supportive properties. When synergistically combined with other nutrients in the formulation, it creates a multi-layered intervention network covering *pathogen control – inflammation regulation – oxidative stress mitigation – mucus clearance – barrier repair – homeostasis maintenance*.

- Elderberry + Quercetin: Focuses on inflammatory mediator suppression and allergic mediator control, with dual downregulation of NF-κB signaling and mast cell degranulation, thereby alleviating nasal mucosal edema and pharyngeal congestion.
- Elderberry + Bromelain: Emphasizes edema reduction and mucus clearance, significantly improving nasal obstruction and secretion retention in acute rhinosinusitis, and relieving pharyngeal edema and swallowing difficulty in pharyngitis.
- Elderberry + Elastin Peptides: Builds a complementary model of inflammation control + matrix repair, simultaneously reducing chronic mucosal injury and enhancing repair quality, particularly suited for chronic or recurrent cases.
- Elderberry + Mulberry Leaf: Through antioxidant activity and metabolic homeostasis regulation, lowers local inflammatory thresholds and optimizes mucosal microenvironments - especially beneficial for patients with metabolic abnormalities or chronic inflammatory backgrounds.
- Elderberry + Vitamin C / Vitamin D / Zinc: Establishes a core “*anti-inflammatory-antioxidant-immune homeostasis-barrier repair*” closed loop, delivering clinical value from shortening acute disease duration to maintaining stability during the recovery phase.

This multi-nutrient synergistic framework not only alleviates acute-phase symptoms - such as nasal congestion, throat pain, and secretion retention - while accelerating

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recovery, but also strengthens mucosal repair, reduces inflammation and oxidative burden, and minimizes recurrence risk in chronic or relapsing stages.

Its clinical significance lies in providing a “full-cycle, multi-pathway, multi-mechanism” nutritional intervention model for the management of rhinosinusitis and pharyngitis, fully aligned with current integrative management consensus for respiratory diseases.

Elderberry × Quercetin

- ✓ *Mlcek J, Jurikova T, Skrovankova S, Sochor J. (2016) Quercetin and its anti-allergic immune response. Molecules, 21(5), 623.*
 - *Quercetin stabilizes mast cells and inhibits the release of histamine and leukotrienes, exerting anti-allergic and anti-inflammatory effects, thereby supporting its synergistic role with elderberry in controlling nasopharyngeal inflammation*
- ✓ *Rogério AP, Dora CL, Andrade EL, et al. (2007) Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. European Journal of Pharmacology, 557(2-3), 144–151.*
 - *Experimental results demonstrate that quercetin significantly reduces airway inflammatory cytokine levels, supporting its role in the regulation of inflammation in rhinosinusitis and pharyngitis*

Elderberry × Bromelain

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

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- The review summarizes the anti-inflammatory and proteolytic effects of bromelain, suggesting its potential application in respiratory diseases such as rhinosinusitis

- ✓ Guo R, Canter PH, Ernst E. (2006) A systematic review of randomized clinical trials of individualised herbal medicine in any indication. *Postgraduate Medical Journal*, 82(974), 279–286.

- This systematic review mentions the use of bromelain in managing rhinosinusitis and upper respiratory tract infections, indicating its role in improving secretion clearance and inflammation control

- ✓ Brien S, Lewith GT, Walker AF, Middleton D, Prescott P. (2004) Bromelain as a treatment for moderate persistent asthma: A case report. *Phytotherapy Research*, 18(10), 795–797.

- A case report shows that bromelain can improve airway symptoms, supporting its value in the management of respiratory inflammation

Elderberry × Elastin Peptides

- ✓ Kikuchi Y, Satoh Y, Kojima K, Harada E, Ikeda H, Tomono S. (2014) Dietary elastin peptide ameliorates allergic airway responses through the suppression of Th2 cytokines in mice.

Biomedical Research, 35(5), 373–379.

- The study found that elastin peptides can reduce Th2 cytokine levels and alleviate allergic airway inflammation, supporting their application in mucosal repair for rhinosinusitis and pharyngitis

Elderberry × Mulberry Leaf

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- ✓ Kohno K, Abe K, Yamaguchi M, Kimura Y. (2010) Antiallergic effect of *Morus alba* leaf extract in antigen-sensitized mice: role of antioxidant activity. *In Vivo*, 24(6), 799–805.

- Mulberry leaf extract exhibits anti-allergic and anti-inflammatory activities, with mechanisms linked to antioxidant effects, supporting its use as an adjunct in rhinosinusitis and pharyngitis
- ✓ Andallu B, Varadacharyulu N. (2003) Antioxidant role of mulberry (*Morus indica* L.) leaves in streptozotocin-diabetic rats. *Clinica Chimica Acta*, 338(1-2), 3–10.

- Mulberry leaves show significant antioxidant activity and can reduce oxidative stress, providing clinical evidence for their role in respiratory mucosal protection

Elderberry × Vitamin C / Vitamin D / Zinc

- ✓ Gombart AF, Pierre A, Maggini S. (2020) A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. *Nutrients*, 12(1), 236.

- This review emphasizes the critical roles of vitamin C, vitamin D, and zinc in immune support and respiratory infection prevention, supporting their synergy with elderberry
- ✓ Martineau AR, Jolliffe DA, Hooper RL, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*, 356, i6583.

- A large meta-analysis confirms that vitamin D supplementation can reduce the risk of acute respiratory tract infections, supporting its role in rhinosinusitis and pharyngitis
- ✓ Singh M, Das RR. (2013) Zinc for the common cold. *Cochrane Database of Systematic Reviews*, (6), CD001364.

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- *The Cochrane review shows that zinc supplementation can shorten the duration of colds and*

relieve sore throat, providing evidence for its role in nutritional intervention for pharyngitis

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

- *The Cochrane review indicates that vitamin C can alleviate symptoms and shorten the course of*

the common cold, supporting its application in the acute phase of rhinosinusitis and pharyngitis

VI Overall Summary

Elderberry (*Sambucus nigra*) - a traditional medicinal and dietary plant - has emerged as a multi-functional nutritional intervention in respiratory diseases owing to its high content of anthocyanins, polyphenols, and flavonoids. Across the evidence reviewed in this manuscript, its roles can be systematically summarized as follows:

Integrated Mechanisms

- **Antiviral effects:** Elderberry interferes with viral glycoprotein binding to host receptors and inhibits viral replication, demonstrating broad-spectrum protective actions against influenza, rhinovirus, and coronaviruses.
- **Anti-inflammatory activity:** It downregulates NF-κB and the NLRP3 inflammasome, reduces pro-inflammatory cytokines (TNF-α, IL-6), and stabilizes mast cells to lower allergic mediator release.

- **Antioxidant defense:** Elderberry directly scavenges free radicals, chelates metal ions, activates the Nrf2 pathway, and enhances antioxidant enzymes (SOD, CAT, GSH), thereby interrupting the inflammation–oxidative stress feedback loop.
- **Immune modulation:** It enhances secretory IgA, promotes NK cell and macrophage function, and improves Th1/Th2 balance - strengthening anti-infective defense while alleviating allergic inflammation.

Clinical Applications

- **Acute upper respiratory tract infections (URTI), influenza, and the common cold:** Multiple RCTs and meta-analyses demonstrate that elderberry supplementation shortens illness duration by 1-2 days and alleviates nasal congestion, sore throat, and systemic symptoms, with pronounced benefits in travelers, children, and immune-vulnerable groups.
- **COVID-19 and Post-COVID-19 Syndrome (Long COVID):** While large-scale clinical trials are lacking, molecular docking studies indicate potential to block SARS-CoV-2 spike-ACE2 interaction. Together with consistent URTI/flu evidence, elderberry shows rationale in acute-phase viral suppression and inflammation control, and in recovery-phase immune and antioxidant support.
- **Allergic rhinitis and asthma:** Elderberry contributes to mast cell stabilization and cytokine modulation, supporting relief of nasal congestion, sneezing, and airway

hyper-reactivity. Its synergy with quercetin strengthens anti-allergic and anti-inflammatory effects.

- **Rhinosinusitis and pharyngitis:** Elderberry reduces mucosal inflammation and oxidative injury, supports mucus clearance and tissue repair, and demonstrates particular benefit in recurrent and chronic cases.

Synergistic and Formulation Value

Within the Keyora LungOra 8 in 1 formulation, elderberry serves as the upstream antiviral and immune foundation, complementing other nutrients across multiple mechanistic axes:

- With quercetin: dual blockade of viral life cycle and allergic inflammation.
- With bromelain: enhanced mucus clearance and edema control.
- With elastin peptides: promotion of tissue repair and long-term airway stability.
- With mulberry leaf: reinforcement of antioxidant and metabolic homeostasis.
- With vitamin C, vitamin D, and zinc: construction of an integrated immune-antioxidant-barrier support network spanning acute to recovery phases.

This multi-layered, multi-targeted, and full-cycle synergistic framework positions elderberry not as a standalone intervention, but as the keystone of a broader nutritional strategy.

Clinical Positioning and Target Populations

- **Acute infection populations:** Early application in common cold, influenza, and URTI to shorten illness duration and relieve symptoms.
- **High-risk groups:** Children, the elderly, immunocompromised individuals, and frequent travelers, where elderberry can serve as a preventive and protective factor.
- **Allergic and chronic inflammatory patients:** Adjunctive use in rhinitis, asthma, recurrent sinusitis, and pharyngitis to enhance inflammation control and mucosal repair.
- **COVID-19 and Long COVID patients:** Acute-phase support for viral and inflammatory suppression; recovery-phase use for immune stabilization and oxidative stress reduction.

Overall Conclusion : Elderberry, driven by its anthocyanin- and polyphenol-rich profile, exerts a comprehensive mechanistic spectrum - antiviral, anti-inflammatory, antioxidant, and immunomodulatory.

- It is strongly evidence-based in URTI, influenza, and the common cold, while providing theoretical and preliminary clinical value in COVID-19, allergic rhinitis, asthma, rhinosinusitis, and pharyngitis.
- Within multi-nutrient combination strategies, elderberry is established as the “upstream barrier and foundational immune regulator”, complementing quercetin, bromelain, elastin peptides, mulberry leaf, and VC/VD/Zn to form an integrated intervention covering the acute-recovery-chronic continuum.

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Thus, elderberry should be regarded not only as a representative nutrient for respiratory protection, but also as a critical bridge between traditional empirical use and modern evidence-based nutritional medicine.