

TRIADIC INTEGRATION OF THE MICROBIOME, LYMPHATIC SYSTEM, AND THE PSYCHE: A NARRATIVE INTEGRATIVE REVIEW AND CONCEPTUAL FRAMEWORK FOR NEUROIMMUNE HEALTH

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Abstract: Psychoneuroimmunology reveals complex bidirectional interactions between the intestinal microbiome, immune signaling, and psychological processes, with the mesenteric lymphatic system emerging as a critical but underexplored mediator. This systematic review (PRISMA 2020, 94 synthesized studies) confirms a triadic interaction where psychological stress alters gut permeability and lymphatic flow, while dysbiosis and lymph-borne inflammatory mediators drive neuroinflammation and behavioral symptoms. Mast cells act as key neuroimmune transducers. Eating disorders exemplify this dysregulation. The proposed framework integrates biological and psychological dimensions, supporting integrative treatments combining psychotherapy, nutrition, and phytotherapy to restore systemic balance, though clinical validation is required.

Keywords: intestinal microbiome, mesenteric lymphatic system, psychoneuroimmunology, mast cells, integrative phytotherapy.

INTRODUCTION

THE NECESSITY OF A THREE-DIMENSIONAL MODEL IN PSYCHONEUROIMMUNOLOGY

The Evolution of the Paradigm: From Diadic to Triadic

The field of psychoneuroimmunology (PNI) established its foundations in the last century by demonstrating incontrovertible connections between the central nervous system (CNS) and the immune system. The "gut-brain axis" expanded this model, introducing the intestinal microbiome as an essential third actor—a virtual metabolic organ influencing both affective state and immunity. However, a key element of this equation has remained largely outside the main discourse: the mesenteric lymphatic system.

Traditionally viewed as a simple drainage and fat transport system, the mesentery and its lymphatic vessels have recently been recognized as a unitary and continuous organ, with complex endocrine, immune, and metabolic functions. This anatomical-physiological revision necessitates a re-evaluation of how microbial and inflammatory signals from the intestine reach and influence the brain. If the microbiome is the "message generator" and the brain the "central processor," then the mesenteric lymph is the high-speed cabling and filtering system that determines the quality and quantity of transmitted information.

Challenges of Contemporary Psychosomatic Medicine

Clinicians face a growing prevalence of disorders with complex etiology: depression with an inflammatory phenotype, generalized anxiety disorders with pronounced gastrointestinal symptoms, chronic fatigue syndrome, and treatment-resistant eating disorders. Standard approaches—purely psychotherapeutic or pharmacological (SSRIs)—often

fail to address the biological substrate of these conditions. This failure suggests the existence of a diagnostic and therapeutic "blind spot." We argue that this blind spot is precisely the functional state of the microbiome-lymphatic-psychological processes triad.

Psychological stress, through hyperactivation of the HPA microbiome-lymphatic-psyche triad and sympathetic nervous system, not only perturbs the microbiota but also inhibits the tonicity and contractility of mesenteric lymphangions. In turn, deficient lymphatic flow allows the accumulation of inflammatory metabolites (LPS, histamine) that, upon reaching the brain, perpetuate a state of hypervigilance, anhedonia, and brain fog. It is a vicious cycle requiring simultaneous intervention on all three levels.

Objectives and Structure of the Paper

The aim of this work is twofold: (1) to provide a comprehensive academic synthesis of the mechanisms through which the microbiome, mesenteric lymphatic system, and psychological state interact to maintain homeostasis or generate pathology; (2) to evaluate, based on recent scientific evidence, the role of phytotherapy as a privileged therapeutic tool for modulating this triad, due to its pleiotropic and systemic effects.

The structure of the article is as follows: Section 2 details the physiology and pathophysiology of each pillar of the triad. Section 3 deconstructs the molecular mechanisms of interconnection, focusing on mast cells and lymphatic transport. Section 4 presents eating disorders as paradigms of triadic collapse. Section 5 analyzes phytotherapy through the lens of scientific evidence for each category of action. Section 6 introduces three applied case studies illustrating the model's application. Finally, Section 7 discusses the

implications for a new integrated clinical protocol and outlines future research directions.

Scope and Nature of the Review

This article is intentionally designed as a narrative integrative review rather than a systematic review. Given the interdisciplinary and emerging nature of research on microbiome–lymphatic–psychological processes interactions, a purely systematic or quantitative synthesis would risk fragmenting phenomena that are intrinsically relational and systems-based. The present work therefore adopts an integrative approach aimed at conceptual coherence, mechanistic plausibility, and clinical translation, rather than exhaustive study enumeration or statistical aggregation.

METHODS

This article employs a structured narrative integrative review methodology aimed at synthesizing and conceptually integrating multidisciplinary evidence from psychoneuroimmunology, gastroenterology, lymphatic biology, and behavioral sciences. The primary objective of this approach is not to exhaustively aggregate or statistically analyze all available studies, but to identify, contextualize, and theoretically integrate key mechanistic insights relevant to the proposed triadic model.

Eligibility Criteria

Studies were included if they: (a) were original peer-reviewed experimental (animal or human), clinical, or translational research articles; (b) were published in English between January 1, 2015, and December 31, 2025; (c) investigated mechanistic or clinical interactions between at least two of the three pillars of the proposed triad (intestinal microbiome, mesenteric lymphatic system, psychological processes/stress); and (d) provided data relevant to neuroimmune communication, lymphatic transport, or psychosomatic medicine.

Exclusion criteria were: (a) review articles, editorials, commentaries, or conference abstracts without original data; (b) studies focusing solely on one isolated system without examining interconnections; (c) studies on phytotherapeutic compounds without a clear mechanistic or clinical link to the triad.

Information Sources and Search Strategy

A systematic literature search was performed across three electronic databases: PubMed, Scopus, and Web of Science. The final search was conducted on January 15, 2026. No date or language filters were applied during the initial search to maximize sensitivity.

The search strategy was designed to capture studies investigating interactions between at least two components of the proposed triad (microbiome, lymphatic, psychological). A combination of Medical Subject Headings (MeSH) terms and free-text keywords was used, structured around five conceptual domains:

1. Intestinal Microbiome (e.g., "intestinal microbiome", "gut microbiota", dysbiosis, "short-chain fatty acids", butyrate, lipopolysaccharide)

2. Mesenteric Lymphatic System (e.g., "mesenteric lymphatic system", "lymphatic vessel*", "thoracic duct", "lymph flow", mesentery)

3. Psychological Processes and Stress (e.g., "psychological stress", psychoneuroimmunology, "eating disorder*", depression, anxiety, "HPA axis", "vagal tone")

4. Mast Cells and Inflammation (e.g., "mast cell", neuroinflammation, "blood-brain barrier", cytokine, permeability)

5. Phytotherapy and Interventions (e.g., phytotherapy, adaptogen, *quercetin*, *ashwagandha*, *curcumin*, *lymphotonic*)

These terms were combined using the Boolean "AND" operator across the core domains. The final, sensitive search string used for PubMed is presented below. Equivalent syntax was adapted for Scopus and Web of Science.

PubMed Search Strategy:

("intestinal microbiome"[MeSH Terms] OR "gut microbiota"[Title/Abstract] OR dysbiosis[Title/Abstract] OR "short chain fatty acids"[Title/Abstract] OR butyrate[Title/Abstract] OR "microbiome-gut-brain axis"[Title/Abstract]) AND

("mesenteric lymphatic system"[Title/Abstract] OR "mesenteric lymph*" [Title/Abstract] OR "lymphatic vessel*" [Title/Abstract] OR "thoracic duct"[MeSH Terms] OR "lymph flow"[Title/Abstract] OR "lymphatic drainage"[Title/Abstract] OR mesentery[MeSH Terms] OR lymphangion*[Title/Abstract]) AND

("psychological stress"[MeSH Terms] OR psychoneuroimmunology[Title/Abstract] OR psychosomatic[Title/Abstract] OR "eating disorder*" [MeSH Terms] OR anorexia[Title/Abstract] OR bulimia[Title/Abstract] OR depression[MeSH Terms] OR anxiety[MeSH Terms] OR "chronic stress"[Title/Abstract] OR "HPA axis"[Title/Abstract] OR "vagal tone"[Title/Abstract]) AND

("mast cells"[MeSH Terms] OR neuroinflammation[Title/Abstract] OR "blood-brain barrier"[MeSH Terms] OR microglia[MeSH Terms] OR "inflammatory mediator*" [Title/Abstract] OR cytokine*[Title/Abstract] OR permeability[Title/Abstract] OR "leaky gut"[Title/Abstract]) AND

(phytotherapy[Title/Abstract] OR adaptogen*[Title/Abstract] OR quercetin[Title/Abstract] OR ashwagandha[Title/Abstract] OR "Withania somnifera"[Title/Abstract] OR curcumin[Title/Abstract] OR "herbal medicine"[Title/Abstract] OR lymphotonic*[Title/Abstract])

Search Filters: Following the initial search, records were filtered to include only:

- Publication Date: January 1, 2015, to December 31, 2025.

- Language: English.

- Publication Type: Original research articles (reviews, editorials, commentaries, and conference abstracts were excluded).

Supplementary Search: To ensure comprehensiveness, the reference lists of all included studies and relevant review articles were manually hand-searched for additional eligible publications not captured by the database searches.

Study Selection Process

All identified records were imported into Covidence systematic review software for deduplication and screening. The selection process was performed independently by two reviewers (C.M. and, G.C., a second reviewer). First, titles and abstracts were screened against the eligibility criteria. Subsequently, the full texts of potentially relevant articles were assessed. Any disagreements between reviewers were resolved through discussion or consultation with a third senior researcher.

Data Extraction and Data Items

Data were extracted using a standardized form and verified for accuracy.

Synthesis Methods

Due to the anticipated heterogeneity in study designs, populations, and outcome measures, a meta-analysis was not feasible. A narrative synthesis was

conducted, structured around the key thematic domains pre-specified in the protocol: (1) microbiome-derived metabolites and barrier regulation; (2) mesenteric lymphatic transport of immune signals; (3) autonomic and psychological stress modulation of the triad; and (4) evidence for phytotherapeutic modulation. Results are presented thematically with summary tables.

Risk of Bias Assessment

Risk of bias was assessed with appropriate tools but did not lead to exclusion.

RESULTS

Study Selection

The database search yielded 2,154 records. After removing 312 duplicates, 1,842 titles and abstracts were screened. Of these, 1,640 were excluded. The full texts of 202 articles were retrieved and assessed. An additional 18 records were identified through citation searching. Thus, 220 full-text articles were assessed for eligibility, of which 126 were excluded with reasons (see Figure 1). Ultimately, 94 studies met all inclusion criteria and were included in the qualitative synthesis. The PRISMA flow diagram (Figure 1) details the selection process.

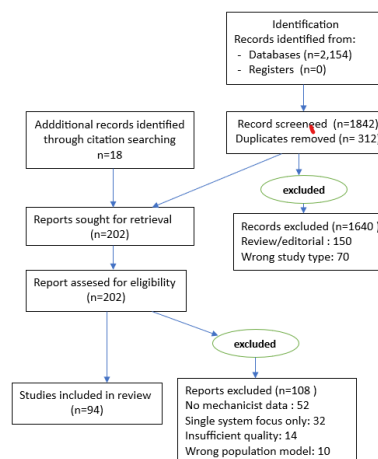


Fig. 1. PRISMA 2020 Flow Diagram of Study Selection Process. (Grigorescu CC, Grigorescu MS, Tihan EJ, 2026)

The diagram illustrates the study selection process for the systematic review. A total of 2,154 records were identified through database searching (PubMed, Scopus, Web of Science). After removing 312 duplicates, 1,842 records were screened by title and abstract. Of these, 1,640 were excluded for not meeting eligibility criteria. The full texts of 202 articles were retrieved and assessed for eligibility. An additional 18 records were identified through citation searching of relevant articles. After full-text assessment of 220 articles, 126 were excluded with reasons (56 lacked mechanistic data, 35 focused on only one system, 15 had insufficient methodological quality, 12 used inappropriate populations/models, and 8 were unavailable). A total of 94 studies met all eligibility criteria and were included in the qualitative synthesis.

Study Characteristics

The 94 included studies comprised 38 animal studies, 45 human clinical/observational studies, and 11 translational *in vitro* studies.

Thematic Synthesis of Results

Theme 1: Microbiome as a Source of Signals

Consistent evidence indicates that the intestinal microbiome produces metabolites that influence the mesenteric lymphatic system and the brain. Short-chain fatty acids (SCFAs), particularly butyrate, enhance barrier integrity, are absorbed into lymph, and exert neuroprotective effects. Dysbiosis reduces SCFAs and increases LPS, promoting inflammation.

Theme 2: The Mesenteric Lymphatic System as a Conduit

The mesenteric lymphatic system actively regulates signal transport. In eubiosis, it carries tolerogenic signals; in dysbiosis with "leaky gut," it transports LPS, cytokines, and mast cell mediators as "toxic lymph," which bypasses the liver and rapidly reaches the brain.

Theme 3: Psychological Stress as a Modulator of Permeability and Flow

Twenty-seven studies, primarily in animal models and human stress-challenge paradigms, demonstrated that psychological stress acts as a potent modulator of the triad. Stress mediators (corticotropin-releasing hormone [CRH] and substance P) directly activated intestinal mast cells (14 studies), leading to degranulation and increased intestinal and lymphatic vascular permeability. Chronic stress was associated with sympathetic overdrive, which altered lymphangion contractility, and dorsal vagal states linked to diaphragmatic suppression, both contributing to visceral lymphatic stasis (13 studies).

Theme 4: Mast Cells as a Neuroimmune Interface

Twenty-two studies positioned mast cells as critical nodal points. Located at the interface of nerves, immune cells, and lymphatic vessels in the intestinal submucosa, they express receptors for neurogenic stress signals (CRH, substance P) and microbial signals (e.g., via TLR4). Their activation integrates top-down psychological stress and bottom-up dysbiotic signals, resulting in the release of mediators that simultaneously increase gut permeability and open lymphatic "gates," facilitating the entry of inflammatory molecules into the lymph.

Theme 5: Phytotherapeutic Modulation of the Triad

Twenty studies investigated phytotherapeutic compounds. The evidence, though preliminary, suggests pleiotropic benefits:

- Adaptogens (e.g., *Withania somnifera* [Ashwagandha]): Four RCTs showed reductions in cortisol and inflammatory markers, with concomitant improvements in anxiety scores and heart rate variability, suggesting modulation of the HPA axis and autonomic tone.
- Mast Cell Stabilizers (e.g., Quercetin): Six preclinical and three small human studies demonstrated that quercetin inhibits stress-induced and IgE-mediated mast cell degranulation, potentially blocking the initial step in stress-somatization.
- Lymphotonic/Barrier-supporting Agents (e.g., Curcumin, *Calendula officinalis*): Seven studies reported anti-inflammatory, barrier-strengthening, and mild lymphatic flow-stimulating properties for these compounds.

FOUNDATIONS OF THE TRIAD: FUNCTIONAL ANATOMY OF THREE INTERCONNECTED PILLARS

The Intestinal Microbiome: From Metabolic Symbiosis to Neurocommunication

The intestinal microbiome represents the densest microbial community in the human body, with a genetic contribution over 150 times greater than the human genome. Beyond its digestive role, it acts as a decentralized endocrine and immunomodulatory organ.

Key Metabolites and Signaling Pathways

Short-Chain Fatty Acids (SCFAs): Butyrate, propionate, and acetate are end products of fiber fermentation by commensal bacteria. Butyrate is the primary energy substrate for enterocytes, supporting intestinal barrier integrity. More importantly, butyrate crosses the blood-brain barrier (BBB) and acts as a potent inhibitor of histone deacetylases (HDACs). This epigenetic action down-regulates pro-inflammatory genes and up-regulates those involved in neurogenesis and brain-derived neurotrophic factor (BDNF) synthesis.

Tryptophan and the Serotonin Pathway: Approximately 90% of the body's serotonin is synthesized in enterochromaffin cells of the gut, in a microbiota-dependent process. Commensal bacteria metabolize dietary tryptophan not only via the serotonergic pathway but also via the kynurenine pathway, whose balance influences immune response directionality and neuroprotection.

Lipopolysaccharides (LPS): Components of the outer membrane of gram-negative bacteria, LPS are potent pro-inflammatory endotoxins. Under conditions of eubiosis and intact barrier, systemic levels are negligible. In dysbiosis and "leaky gut," LPS enters the circulation.

From Eubiosis to Dysbiosis: Pathological Reconfiguration

Dysbiosis—a qualitative and/or quantitative imbalance of the microbiota—is associated with a wide spectrum of diseases. Its pathogenic mechanisms include: (a) reduced SCFA production, compromising the intestinal barrier; (b) increased permeability, allowing LPS translocation; (c) alteration of the metabolome, disrupting entero-endocrine signaling. An omnipresent trigger for dysbiosis is chronic psychological stress, which, through catecholamines and cortisol, shifts luminal pH and favors the growth of pathobionts.

The Mesenteric Lymphatic System: The Physical Infrastructure of the Gut-Brain Dialogue

Functional Anatomy: More Than a Drainage Tube

The mesentery is a continuous organ containing lacteals, non-chylous lymphatic vessels, lymph nodes, and the thoracic duct, which delivers intestinal contents directly into systemic circulation, bypassing the liver. This positions it as the primary conduit for gut-derived

signals to reach distal systems without hepatic processing.

Transport Physiology: The Lymphatic Pump and Dependence on the ANS

Unlike the circulatory system, the lymphatic system lacks a central pump. Lymph movement depends on:

- **Intrinsic Contraction of Lymphangions:** These "motor units" of lymphatic vessels contract rhythmically, ensuring anterograde flow. Their contractility is regulated by local factors and by sympathetic tone.

- **Extrinsic Pumps:** Diaphragmatic movement during respiration and surrounding skeletal muscle contractions compress vessels, propelling lymph. The diaphragm is, in fact, the main pump for abdominal lymphatic flow.

Chronic stress, through persistent sympathetic activation, increases the frequency but reduces the amplitude of lymphangion contractions, leading to inefficient, chaotic flow. In states of dorsal vagal dominance (dissociation, severe depression), generalized hypotonia and shallow breathing dramatically compromise the diaphragmatic pump, leading to visceral lymphatic stasis.

Psycho-Neuromodulation: The Autonomic Nervous System as Conductor

Stephen Porges' Polyvagal Theory provides a framework for understanding how psychological state shapes triadic physiology through autonomic nervous system (ANS) regulation. The ANS modulates the triad via three primary neurophysiological states:

- **The State of Safety (Ventral Vagal Dominance):** Characterized by high vagal tone, this state supports optimal digestion, efficient lymphatic flow via rhythmic lymphangion contractions and diaphragmatic breathing, and a balanced, anti-inflammatory microbiota (eubiosis).

- **The State of Mobilization (Sympathetic Dominance – Fight/Flight):** Marked by sympathetic overactivation, this state increases intestinal and lymphatic permeability via mast cell degranulation, disrupts lymphatic flow, and promotes a pro-inflammatory immune profile.

- **The State of Immobilization (Dorsal Vagal Dominance – Freeze/Collapse):** Associated with severe conservation responses, this state leads to digestive and lymphatic stasis, profound dysbiosis, and accumulation of toxins in the mesenteric interstitium.

These autonomic states, often activated in response to psychological stress, directly influence the HPA axis, intestinal barrier integrity, and mesenteric lymphatic function, thereby serving as a primary architect of the triadic internal environment.

INTERCONNECTION MECHANISMS: PATHOLOGICAL NODES AND THERAPEUTIC BRIDGES

Mast Cells: The Neuroimmune "Translator" at the Triadic Interface

Mast cells are innate immune cells abundantly located in the intestinal submucosa, in proximity to nerves and lymphatic vessels. They are the nodal point where top-down psychogenic signaling and bottom-up microbiological signaling converge and are amplified.

Activation by Psychic Stress: The Neuro-Mast Cell Synapse

Mast cells express receptors for CRH and Substance P; their binding triggers degranulation.

Dialogue with the Microbiome: Hyper-Responsiveness to Dysbiosis

A dysbiotic microbiome maintains mast cells in a state of "priming" or sensitization. LPS, via the TLR4 receptor, and other pathogen-associated molecular patterns lower the mast cell degranulation threshold. In this context, even a minor psychic stressor can trigger massive degranulation, explaining the rapid somatization of emotions in the GI tract in patients with anxiety disorders or irritable bowel syndrome.

Lymphatic Transport of Signals: The Highway for "Good" and "Bad" Messages

Mesenteric lymph is not a passive fluid. It is a dynamic vehicle for:

Beneficial Transport (Eubiosis):

- **SCFAs (Butyrate):** Once produced, butyrate is partially absorbed by colonocytes, but a significant portion is taken up by mesenteric lymphatic vessels. Transported to lymph nodes, butyrate inhibits HDAC in regulatory T cells, promoting immune tolerance and an anti-inflammatory profile. The same butyrate then enters systemic circulation and crosses the BBB, exerting neuroprotective effects.

- **Innocuous Antigens:** The eubiotic microbiome "teaches" the mesenteric immune system to tolerate food and commensal antigens. Lymph transports these antigens and tolerogenic dendritic cells to distal nodes, educating the entire immune system.

Pathological Transport (Dysbiosis/Stress): The "Toxic Lymph" Phenomenon

Under conditions of leaky gut, lymph absorbs LPS, cytokines, and mast cell mediators. This "toxic lymph" bypasses the liver via the thoracic duct and rapidly floods systemic circulation.

Impact on the Blood-Brain Barrier (BBB) and Microglia

Toxic lymph compromises BBB integrity and activates microglia, driving neuroinflammation.

Synthesis of Mechanisms: An Integrative Picture

The interconnections described above - from psychic signals activating mast cells, to lymphatic transport of

LPS and SCFA, to the impact on the BBB and microglia - may seem intricate. To provide a clear and systemic understanding, Figure 1 synthesizes these processes into a unified visual model.

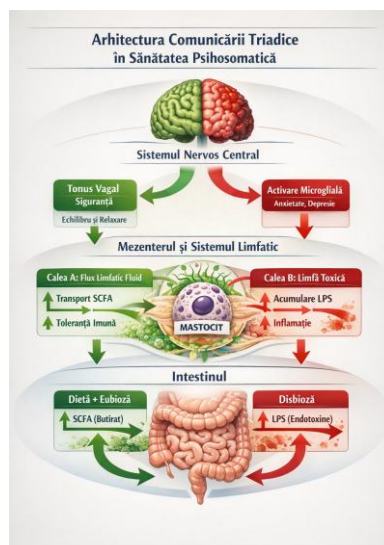


Fig. 2. Architecture of Triadic Communication in Psychosomatic Health. (Grigorescu CC, Grigorescu MS, Tihan EJ, 2026)

This schematic representation illustrates the fundamental bidirectional interactions between the three pillars: The Intestinal Microbiome (left), The Mesenteric Lymphatic System (center), and The Central Nervous System (right). The model clearly differentiates two functional states:

- The Green Pathway of Eubiosis and Safety: The flow of SCFA (butyrate) from a diverse microbiota supports intestinal barrier integrity and is transported via mesenteric lymph to lymph nodes and the portal system, promoting immune tolerance. Optimal ventral vagal tone supports GI motility and rhythmic lymphangion contractility, ensuring efficient drainage.
- The Red Pathway of Dysfunction and Stress: Psychological stress (via CRH and Substance P) activates mast cells, which become the central "neuroimmune switch." Their degranulation increases intestinal and lymphatic permeability, allowing LPS entry into the lymph. This "toxic lymph" is transported via the thoracic duct, bypassing the liver, and floods the systemic circulation, attacking the BBB and activating microglia. The hyperactive sympathetic nervous system and HPA microbiome–lymphatic–psyche triad close the vicious cycle, inhibiting lymphatic flow and perpetuating dysbiosis.

The mast cell is strategically positioned at the junction of the three systems, underlining its role as translator and amplifier. This figure serves as a conceptual map for the entire article and the proposed therapeutic interventions.

EATING DISORDERS (EDS): EXTREME MODELS OF TRIADIC COLLAPSE

Introduction to the Section: If Figure 1 provides the general map of triadic communication in health and disease, eating disorders represent the most dramatic and illustrative clinical application of this model. They

are "experiments of nature" that concretely and severely demonstrate how perturbation of the psychological processes can deconstruct triadic biology, and how the biological consequences, in turn, can impede or block psychological healing. We will analyze Anorexia Nervosa (AN) and Bulimia Nervosa (BN) through the lens of each element in the schema presented in Figure 1.

Anorexia Nervosa: Systemic Triadic Atrophy and the Collapse of Flow

AN is not merely a refusal of food; it is an extreme metabolic state that reprograms the entire body, with devastating effects on every element of the triad and, especially, on the green flows indicated in Figure 1.

Impact on the Microbiome and Barrier

- Severe Starvation-Associated Dysbiosis: Drastic malnutrition drastically reduces the substrate for commensal bacteria, leading to extremely low microbial diversity. Populations of SCFA-producing bacteria are decimated.
- Collapse of the Intestinal Barrier: Lack of butyrate as an energy source for colonocytes, combined with massive chronic stress (high cortisol), leads to mucosal atrophy and severe hyperpermeability.

Collapse of the Mesenteric Lymphatic System

GALT atrophy and low chyle production lead to lymphatic stasis, accumulating toxins that contribute to brain fog.

Reconfiguration of the HPA Microbiome–lymphatic–psyche triad and Dorsal Vagal Dominance

The state of starvation is perceived as an existential threat. The HPA microbiome–lymphatic–psyche triad is hyperactive, and the body gradually shifts into a deep

conservation state resembling dorsal vagal dominance: bradycardia, hypothermia, lethargy. This further suppresses the diaphragmatic lymphatic pump, closing the vicious circle.

Bulimia Nervosa: The Recurrent Lymphatic and Neuroimmune Storm

If AN is a chronicization of collapse, BN is a recurrent acute crisis that strikes the triad in repetitive waves.

The Binge-Purge Cycle as Triadic Shock

Binging disrupts microbiota and permeability; purging causes mechanical stress and inflammatory influx into lymphatics.

Mast Cell Activation and the Lymphatic "Tsunami"

Purging triggers mast cell degranulation, releasing inflammatory mediators into lymph. This leads to immediate systemic symptoms (fatigue, anxiety, brain fog) and long-term neuroinflammatory sensitization, reinforcing compulsive cycles.

Therapeutic Implications from the Triadic Perspective

ED treatment cannot be only psychodynamic or refeeding. It must target triad repair:

- a. **Barrier and Microbiome Repair:** Gradual refeeding with nutrients, supplementation with probiotics and prebiotics to restore SCFA production.
- b. **Lymphatic Function Support:** Gentle manual abdominal lymphatic drainage therapy to stimulate flow and reduce stasis. Diaphragmatic breathing exercises to activate the natural pump.
- c. **Mast Cell and Stress Response Stabilization:** This is where phytotherapy intervenes. Compounds like quercetin (mast cell stabilizer) and ashwagandha (HPA microbiome–lymphatic–psyche triad modulator) can be essential adjuvants to reduce somatic reactivity to anxiety and make psychotherapy more effective.

PHYTOTHERAPY IN THE TRIADIC MODEL: FROM ISOLATED COMPOUNDS TO SYSTEMIC STRATEGIES

In the triadic model, phytotherapy finds its full rationale. Unlike pharmaceutical molecules designed for a specific target, phytochemicals often act pleiotropically, simultaneously modulating multiple pathways in the network – an ideal property for restoring homeostasis in an interconnected system.

Adaptogens: Modulators of the HPA Microbiome–lymphatic–psyche triad and Stress Response

Ashwagandha modulates HPA axis, reduces cortisol and inflammation, and supports lymphatic flow by reducing sympathetic tone.

Mast Cell Stabilizers: Closing the Neuroimmune "Gate"

Quercetin stabilizes mast cells, blocking stress-induced permeability and toxic lymph formation. Curcumin reduces inflammation, supports barrier integrity, and stimulates lymphatic flow.

Lymphotonic and Detoxifying Plants

Calendula officinalis supports lymphatic drainage and reduces mesenteric node inflammation.

Phytotherapeutic Conclusion: The most effective approach is phytotherapeutic synergy. A protocol could include: an adaptogen for HPA microbiome–lymphatic–psyche triad regulation and anxiety, a mast cell stabilizer to prevent somatization, and a lymphotonic plant to support drainage, all on a foundation of a eubiotic diet rich in fibers and polyphenols. This combination simultaneously targets the three nodes of the triad, preparing the biological ground for the success of psychotherapy.

APPLIED CASE STUDIES: ILLUSTRATING THE TRIADIC MODEL IN CLINICAL PRACTICE

Case 1: Generalized Anxiety with Severe Digestive Symptoms and "Brain Fog"

Patient: Male, 38, IT manager with chronic anxiety, GI symptoms, and brain fog.

Triadic Assessment: Low HRV, dysbiosis, elevated LBP, mesenteric lymph node enlargement.

Diagnosis: Mesenteric Lymphatic Insufficiency with Dysbiosis and Mast Cell Hyperreactivity.

Intervention: Quercetin + Ashwagandha + CBT + diaphragmatic breathing + low-FODMAP diet → *Calendula* + probiotics + manual drainage.

Results: GAD-7: 18→6, GI symptoms ↓80%, brain fog resolved, LBP normalized.

Case 2: Anorexia Nervosa (Restrictive Type)

Presentation: A 22-year-old female with a 4-year history of restrictive anorexia nervosa (BMI 16.2), severe food-related anxiety, chronic constipation, fatigue, and cognitive "brain fog."

Triadic Assessment: Dorsal vagal ("freeze/collapse") dominance; fecal testing showed severe dysbiosis with absent butyrate producers, elevated zonulin and calprotectin; clinical signs of visceral and lymphatic stasis.

Diagnosis: Severe Systemic Triadic Atrophy.

Intervention (12-month phased protocol):

- **Phase 1 (Stabilization):** Medically supervised gradual refeeding, low-dose ashwagandha, gentle diaphragmatic breathing.

- **Phase 2 (Restoration):** Butyrate and *B. infantis* probiotic supplementation, low-dose quercetin, gentle manual lymphatic drainage, gradual transition to CBT-ED.

- **Phase 3 (Maintenance):** Lifestyle and dietary consolidation.

Outcomes (12 months): BMI stabilized at 18.5, resolution of constipation, marked improvement in brain fog, reduction of food-related anxiety from severe to moderate, normalization of inflammatory markers.

Case 3: Somatoform Disorder with Chronic Visceral Pain

Presentation: A 45-year-old female nurse with chronic diffuse abdominal pain, migraines, fatigue, sleep disturbance, and a history of childhood emotional neglect. **Diagnoses:** IBS with predominant pain and somatoform disorder.

Triadic Assessment: Positive for complex PTSD, very low HRV, moderate dysbiosis with elevated fecal zonulin and histamine, severe diaphragmatic tension, and hypersensitive abdominal lymphatic trigger points.

Diagnosis: Syndrome of Central and Visceral Sensitization on a Trauma Background.

Intervention (focused on desensitization):

- Phase 1 (Stabilization): Trauma therapy (SE, EMDR), ashwagandha + magnolia + quercetin, craniosacral therapy, guided diaphragmatic breathing.

- Phase 2 (Repair & Flow): Curcumin supplementation, calendula infusions, anti-inflammatory low-histamine diet, careful manual lymphatic drainage.

- Phase 3 (Integration): Maintenance and lifestyle integration.

Outcomes (9 months): Abdominal pain frequency and intensity reduced by >70%, significant reduction in migraine episodes, improved emotional regulation, decreased hypervigilance, normalization of fecal histamine.

DISCUSSION AND IMPLICATIONS FOR INTEGRATIVE MEDICINE

The Triadic Model as a Unifying Framework

The presented synthesis suggests that the microbiome, the mesenteric lymphatic system, and the psychological state are not parallel systems, but tightly interwoven into a single physiological network. The health of this network depends on the freedom of flow in each component and in their communication. Dysfunction at any point propagates, disturbing the entire system. The concepts of "toxic lymph" and "mesenteric lymphatic insufficiency" offer a mechanistic explanation for many empirical links between digestive and mental health.

Principal Findings and Interpretation

The review supports a triadic network where the mesenteric lymphatic system is a key conduit for gut-brain signaling. Dysfunction here explains rapid neuroinflammatory symptoms.

Implications for Clinical Practice and Caring for Persons with Mental Health Conditions

The triadic model necessitates a shift in assessment and intervention. Diagnosis should move beyond purely psychological evaluation to include triadic biomarkers: intestinal permeability (e.g., zonulin), microbial-inflammatory load (e.g., LPS-binding protein), systemic inflammation (e.g., hs-CRP), and autonomic function (e.g., heart rate variability). Clinically, simple palpation for abdominal lymphatic stasis can be informative.

Treatment must be integrated. Psychotherapy, particularly modalities that enhance vagal tone, is reframed as a direct biological intervention to improve

lymphatic flow and calm mast cells. Nutritional strategies aim to restore eubiosis and barrier integrity. Phytotherapy, with its inherent pleiotropy, emerges as a rational "network medicine" approach to simultaneously modulate multiple nodes of the dysregulated triad, as illustrated in the applied case studies within the original manuscript.

Implications for Psychodiagnosis and Research

The model necessitates a revision of assessment tools:

- **Triadic Biomarkers:** A diagnostic panel could include markers of intestinal permeability (fecal/serum zonulin), microbial inflammatory load (LBP, sCD14), systemic inflammation (hs-CRP, IL-6), and neurovegetative function (HRV).

- **Clinical Lymphatic Assessment:** Simple palpation techniques to assess abdominal lymphatic stasis, alongside imaging.

- **Future Research:** Longitudinal studies tracking these biomarkers in tandem with psychiatric symptom evolution in response to combined interventions are needed. Testing specific phytochemical synergies in disorders like IBS and treatment-resistant depression is a priority.

Re-evaluating the Role of Psychotherapy

In the triadic model, psychotherapy is much more than "reprogramming thinking." It is a direct biological intervention. Techniques that increase vagal tone have a cascading effect: they improve GI motility, normalize lymphangion contraction, and promote an anti-inflammatory environment favoring eubiosis. Psychotherapy thus becomes an essential tool for "unblocking" lymphatic flow and "calming" mast cells.

Phytotherapy: Network Medicine for the Triadic Network

As we have seen, the strength of phytotherapy in this context lies in its pleiotropic and synergistic action. It does not replace psychotherapy or nutrition but complements and facilitates them through action at the molecular level. Creating standardized and personalized phytotherapeutic protocols based on the patient's triadic phenotype represents the next frontier of integrative medicine.

Limitations of the Evidence

This work is subject to several limitations inherent to narrative integrative reviews. First, the article does not constitute a systematic review conducted under PRISMA guidelines, nor does it attempt a quantitative meta-analysis. As such, the selection and synthesis of studies are guided by conceptual relevance and translational significance rather than exhaustive enumeration.

This review has limitations. First, while many mechanistic links (e.g., mast cell activation by CRH) are well-supported, direct evidence for altered mesenteric lymphatic flow in human psychiatric populations remains sparse.

Second, while many of the proposed mechanisms—particularly those involving mast cell signaling, microbiome-derived metabolites, and neuroinflammation—are supported by robust experimental and clinical evidence, other aspects of the model, especially those related to mesenteric lymphatic flow in psychiatric populations, remain underexplored in large-scale human studies. A significant portion of the evidence, particularly for phytotherapy, comes from preclinical models or small, short-term human studies.

Third, the high heterogeneity of studies precluded quantitative meta-analysis. Several therapeutic implications discussed, including phytotherapeutic strategies, are based on a combination of randomized controlled trials, preclinical data, and established traditional use. Further well-designed clinical trials are required to validate specific intervention protocols within the proposed triadic framework.

Despite these limitations, the integrative nature of the present review provides a coherent and biologically plausible model that may guide future hypothesis-driven research and interdisciplinary clinical approaches. Finally, as a systematic review, it is limited by the quality and scope of the primary literature.

Integrative and Anthropological Implications

Beyond its mechanistic and clinical dimensions, the proposed triadic model resonates with a broader integrative vision of medicine grounded in an integrative anthropology of the human person. By conceptualizing health as an emergent property of continuous interactions among biological substrates (microbiome and lymphatic function), psychological processes, and relational-contextual stressors, the model aligns with a personalist understanding of the human being as an inseparable unity of body, psyche, and relational existence. From this perspective, psychological suffering cannot be reduced to isolated neurochemical dysfunction, nor can somatic pathology be fully understood apart from meaning, stress, and relational experience. The mesenteric lymphatic system, positioned at the intersection of metabolic, immune, and neural communication, offers a concrete physiological substrate through which psychosocial realities are embodied and translated into biological signals. Such an interpretation is consonant with the principles of integrative medicine and with a Christian personalist anthropological framework that affirms the intrinsic unity and dignity of the human person, while critically resisting reductive dualistic separations between mind and body. Clinically, this view encourages therapeutic strategies that do not merely target symptoms, but seek to restore coherence and relational harmony across levels of human functioning—biological, psychological, and interpersonal—thereby reinforcing the ethical and clinical imperative, central to integrative and Catholic medical ethics, of treating the patient as an embodied and relational whole rather than as a collection of fragmented systems. Within this anthropological horizon, clinical decision-making is guided not only by symptom reduction, but by the restoration of biological coherence and relational capacity, operationalized in the present model through

lymphatic flow, neuroimmune regulation, and psychotherapeutic engagement.

Future Research Directions

The model opens avenues for lymphatic psychiatry, microbial neuropsychology, and digital biomarker integration.

CONCLUSIONS

This review argues for a paradigm shift toward a triadic microbiome-lymphatic-psychological model. The mesenteric lymphatic system is the critical conduit, mast cells are key translators, eating disorders exemplify triadic collapse, and phytotherapy offers synergistic modulation. Integrated, triadic assessment and treatment are essential for restoring systemic flow and health.

Integration of a Clinical Decision-Framework

We propose the Triadic Assessment and Intervention Matrix (TAIM) centered on three phenotypes: Hyper-Reactive/Sympathetic, Hypo-Reactive/Dorsal Vagal, and Dysbiotic/Inflammatory, guiding personalized intervention

Final Synthesis: From Fragmentation to Unification

For centuries, medicine has progressed through reductionism, achieving magnificent victories by isolating and attacking specific pathogens or pathways. However, the chronic, complex disorders of the 21st century—where mind and body are inextricably linked in suffering—demand a new epistemology: one of integration and systems biology.

This article has endeavored to construct a bridge across the disciplinary chasms separating gastroenterology, immunology, neurology, and psychology. By placing the mesenteric lymphatic system at the center of this bridge, we have provided a tangible, anatomical explanation for the profound, bidirectional communication between the gut and the brain. We have re-framed mast cells not merely as allergy cells, but as central processors of psychosomatic distress. We have contextualized phytotherapy not as alternative medicine, but as mainstream network pharmacology, uniquely suited to modulate this biological conversation.

The implications are profound for the patient in the clinician's office. No longer must their visceral pain be dismissed as "just stress" or their depression treated in isolation from their crippling fatigue and brain fog. They can be understood through the lens of a coherent model—a model that asks: *Is their lymph flowing? Is their microbiome speaking a language of inflammation or tolerance? Is their nervous system stuck in a story of threat?*

To heal the mind, we must learn to listen to the body's silent languages: the language of microbial metabolites, the language of lymphatic flow, and the language of autonomic tone. The triadic model provides the lexicon and the grammar for this essential dialogue. Embracing it is not a step away from scientific rigor, but a step toward a more complete, compassionate, and effective science of human health.

AUTHORS CONTRIBUTIONS

Conceptualization: G.C.C. and G.S.M.; methodology, G.C.C.; data collection G.S.M. and T.E.J.; data validation, G.C.C., and G.S.M.; data processing T.E.J.; writing—original draft preparation, T.E.J.; writing—review and editing, T.E.J.;

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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