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THE MICROBIOTA–GUT–BRAIN AXIS IN STRESS AND ANXIETY: INTEGRATING NEURAL, ENDOCRINE, IMMUNE AND METABOLIC EVIDENCE

Amita Tripathi*[1], Dilip Nalage[2], Aradhna Purohit[3], Priya More[4], Prof. Dr. Rahul Palshetkar[5]

[1]PG Scholar, Dept. of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh.
[2]Professor, Department of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh.
[3]Professor Department of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh
[4]Assistant Professor, Department of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh.
[5]HOD, Department of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh.

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***Corresponding Author: Amita Tripathi**
PG Scholar, Dept. of Samhita & Siddhanta, Pt. Shivshaktilal Ayurveda Medical College Ratlam Madhya Pradesh.
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ABSTRACT

Background: Stress and anxiety are complex neuropsychiatric conditions influenced by genetic, environmental, neuroendocrine, immune, and behavioural factors. Increasing evidence highlights the microbiota–gut–brain axis (MGBA) as an important bidirectional communication pathway linking the gastrointestinal tract and central nervous system through neural, endocrine, immune, metabolic, and barrier-mediated mechanisms. **Objective**: This review synthesizes recent evidence on the mechanisms connecting gut microbiota with psychological stress and anxiety, focusing on the hypothalamic–pituitary–adrenal axis, vagal signalling, intestinal and blood–brain barriers, microbial metabolites, immune activation, neurotransmitter pathways, and dietary influences. Evidence for microbiota-targeted interventions, including probiotics, prebiotics, synbiotics, postbiotics, and dietary approaches, is also evaluated. **Methods**: A focused narrative review of recent literature indexed in PubMed and major biomedical databases was conducted, prioritizing studies published from 2021–2026, including systematic reviews, meta-analyses, randomized controlled trials, and mechanistic studies. **Results**: Evidence supports a bidirectional relationship between stress and gut microbial function. Stress can alter intestinal motility, permeability, immunity, and microbial ecology, while microbial metabolites and signalling pathways may influence neuroendocrine, immune, vagal, and brain-barrier functions. A 2023 meta-analysis of 29 randomized controlled trials involving 2,035 participants reported significant reductions in anxiety following probiotic and synbiotics interventions, although substantial heterogeneity was observed. **Conclusion**: The MGBA represents a promising interface between psychological stress and gastrointestinal physiology. However, clinical translation requires further mechanistic, longitudinal, and personalized research.

KEYWORDS: Gut–Brain Axis; Microbiota; Anxiety; Psychological Stress; Psych Biotics; Short-Chain Fatty Acids; Hypothalamic–Pituitary–Adrenal Axis; Vagus Nerve; Neuroinflammation; Microbial Metabolites; Probiotics: Mental Health.

1. INTRODUCTION

Stress is a fundamental adaptive physiological response that enables an organism to respond appropriately to perceived environmental or internal challenges. Acute stress may enhance vigilance, mobilize metabolic resources, and facilitate appropriate behavioural responses. However, when stress becomes persistent, excessive, or inadequately regulated, sustained activation of neuroendocrine, autonomic, and immune pathways may contribute to disturbances in sleep, cognition, gastrointestinal function, and emotional regulation. Anxiety similarly exists along a continuum, ranging from adaptive anticipatory responses to persistent, excessive, and functionally impairing fear and worry.

Consequently, the biological basis of anxiety extends beyond the central nervous system and involves complex interactions among multiple physiological systems.

One of the most rapidly evolving areas of research in this field is the microbiota–gut–brain axis (MGBA). The gastrointestinal tract harbours a dense and metabolically active microbial ecosystem capable of synthesizing, transforming, and modulating numerous biologically active signalling molecules. These microorganisms interact continuously with intestinal epithelial cells, enteroendocrine cells, immune cells, and enteric neurons. Signals originating within this environment can subsequently influence peripheral physiology and central nervous system function. Conversely, the brain regulates gastrointestinal activity through autonomic, neuroendocrine, and behavioural pathways, thereby establishing a dynamic and bidirectional communication network between the gastrointestinal tract and the brain.[1-3]

Recent conceptual advances have shifted the understanding of the MGBA from a relatively simple model in which the gut microbiome influences brain function toward a more integrated framework involving the microbiota, intestinal barrier, immune system, peripheral nervous system, and central nervous system as interconnected components of a complex physiological network. The gut sensory system, including epithelial chemosensory cells and their associated neural pathways, represents an important interface through which microbial and nutritional signals may be transmitted to the nervous system.[3] Furthermore, the intestinal barrier, blood–brain barrier, and blood–cerebrospinal fluid barrier regulate the movement of microbial metabolites, immune mediators, and other signalling molecules between physiological compartments, thereby contributing to the maintenance of systemic and neurological homeostasis.[2]

Stress provides a particularly informative physiological model for investigating this bidirectional communication. Experimental and clinical evidence indicates that psychological stress can influence intestinal motility, mucus secretion, epithelial permeability, immune signalling, and the composition and functional activity of the gut microbial community.[4-6] Conversely, microbial-derived metabolites and molecular components may modulate neuroendocrine and immune responses, thereby influencing stress responsiveness and emotional behaviour.[4-6] Notably, a recent mechanistic study published in *Cell* provided evidence supporting the brain-to-gut direction of this communication by identifying a neural pathway linking stress-sensitive circuits within the central amygdala to duodenal glands, intestinal *Lactobacillus* populations, and mucosal immune responses.[7]

At the clinical level, however, the available evidence remains heterogeneous. Individuals experiencing anxiety or depressive symptoms may demonstrate alterations in gut microbial composition and function; nevertheless, no single microbial signature has been consistently established as a defining feature of anxiety. Multiple host and environmental factors, including medication use, dietary patterns, metabolic status, sleep, age, sex, geographical location, and lifestyle, can substantially influence the gut microbiome and may confound observed associations between microbial alterations and psychiatric symptoms.[8-10] Accordingly, recent perspectives, including those published in *Nature Mental Health*, have emphasized the importance of distinguishing causal, correlative, and bidirectional relationships rather than assuming that every observed microbial alteration represents a pathogenic mechanism.[9]

This distinction is particularly relevant to the development and evaluation of microbiota-targeted therapeutic strategies. Probiotics, prebiotics, synbiotics, postbiotics, and other microbiota-directed approaches, including those collectively described as psychobiotics, have attracted considerable scientific interest. Meta-analytic evidence suggests that selected interventions may produce reductions in anxiety symptoms; however, individual randomized controlled trials have reported both beneficial and null outcomes.[11-14] Such variability suggests that therapeutic efficacy may depend on specific microbial strains, formulation, dosage, intervention duration, host characteristics, dietary context, and behavioural factors rather than merely on the presence of broadly defined “beneficial bacteria.”

Therefore, the objective of this review is to integrate contemporary evidence regarding the relationship between the microbiota–gut–brain axis, psychological stress, and anxiety, with particular emphasis on underlying biological mechanisms and their translational implications. Specific attention is given to the hypothalamic–pituitary–adrenal (HPA) axis, autonomic and vagal signalling, intestinal and brain barriers, microbial metabolites, immune-mediated pathways, dietary influences, and microbiota-targeted interventions. This integrated perspective may contribute to a more comprehensive understanding of the role of the MGBA in stress and anxiety and help identify priorities for future mechanistic and clinical research.

2. METHODS

2.1 Review Design

A structured narrative review was undertaken to critically synthesize contemporary evidence regarding the bidirectional relationship between the microbiota–gut–brain axis (MGBA), psychological stress, and anxiety. The review focused on underlying mechanistic pathways, human clinical evidence, and emerging microbiota-targeted therapeutic interventions. Emphasis was placed on neuroendocrine signalling, autonomic and vagal pathways, intestinal and blood–brain barrier integrity, immune mechanisms, microbial metabolites,

dietary influences, and microbiota-directed interventions, including probiotics, prebiotics, synbiotics, and postbiotics.

The review was designed as a narrative evidence synthesis rather than a systematic review or meta-analysis, owing to the substantial methodological heterogeneity observed across the available literature. This heterogeneity encompasses differences in study populations, experimental models, microbiome assessment and analytical techniques, psychological outcome measures, intervention protocols, and follow-up durations. The methodological framework was structured to promote transparency in literature identification, study selection, data organization, and interpretation of the available evidence.

2.2 Research Question and Objectives

The review was guided by the following primary research question:

How does the microbiota–gut–brain axis contribute to the development or modulation of psychological stress and anxiety, and what is the current evidence supporting microbiota-targeted therapeutic approaches?

The specific objectives were to:

1. Examine the bidirectional relationship between psychological stress and gut microbial ecology.
2. Synthesize evidence concerning hypothalamic–pituitary–adrenal (HPA) axis, autonomic, and vagal signalling.
3. Evaluate the potential roles of intestinal and blood–brain barrier function and immune-mediated signalling.
4. Examine microbial metabolites, including short-chain fatty acids and tryptophan-derived metabolites, as potential mediators of MGBA signalling.
5. Critically evaluate human evidence linking gut microbiota with psychological stress and anxiety.
6. Summarize contemporary clinical evidence concerning probiotics, prebiotics, synbiotics, and postbiotics.
7. Identify major methodological limitations and priorities for future research investigating the microbiota–gut–brain axis.

2.3 Literature Search Strategy

A comprehensive literature search was conducted using major biomedical and multidisciplinary electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science Core Collection. Where available, Embase was considered as an additional biomedical database. Reference lists of relevant review articles and eligible primary studies were also manually screened to identify potentially relevant publications that may not have been retrieved through the electronic database searches.

The literature search encompassed publications dated from 1 January 2021 to 20 September 2026, thereby maintaining the predefined five-year evidence window for the present review.

The search strategy incorporated a combination of controlled vocabulary and free-text terms related to gut microbiota, psychological stress, anxiety, relevant biological mechanisms, and microbiota-targeted interventions. A representative PubMed search strategy was as follows:

(“gut microbiota” OR “gut microbiome” OR “intestinal microbiota” OR “intestinal microbiome” OR “microbiota-gut-brain axis” OR “gut-brain axis”) AND (“stress” OR “psychological stress” OR “chronic stress” OR “stress response” OR anxiety OR “anxiety disorder*”) AND (“HPA axis” OR cortisol OR vagus OR “vagal signalling” OR “intestinal barrier” OR “blood-brain barrier” OR inflammation OR neuroinflammation OR “short-chain fatty acid*” OR SCFA* OR tryptophan OR metabolite* OR probiotic* OR prebiotic* OR synbiotic* OR postbiotic* OR psychobiotic*).

Equivalent database-specific search strategies were adapted for Scopus and Web of Science according to their respective indexing systems and search syntax.

2.4 Eligibility Criteria

Studies were considered eligible for inclusion when they fulfilled the predefined eligibility criteria.

Inclusion Criteria

1. Publications available between January 2021 and September 2026.
2. Human studies, including observational, cohort, cross-sectional, and randomized controlled studies.
3. Relevant experimental animal studies providing mechanistic evidence directly related to the MGBA, psychological stress, or anxiety.
4. Systematic reviews, meta-analyses, and high-quality narrative or mechanistic reviews relevant to the objectives of the present review.
5. Studies investigating gut microbiota or the gut microbiome in relation to psychological stress, anxiety, or stress-related behavioural phenotypes.
6. Studies investigating biological pathways linking the gut microbiota with the nervous system, including HPA-axis signalling, vagal pathways, immune signalling, intestinal barrier integrity, blood–brain barrier function, and microbial metabolites.
7. Clinical intervention studies evaluating probiotics, prebiotics, synbiotics, postbiotics, or other microbiota-targeted interventions in relation to stress, anxiety, or related psychological outcomes.
8. Publications available in the English language.
9. Articles published in peer-reviewed journals.

Exclusion Criteria

The following publications were excluded from the review:

1. Publications outside the predefined 2021–2026 period.
2. Conference abstracts lacking sufficient methodological or outcome information.
3. Editorials, letters, commentaries, and opinion articles without substantive original or synthesized evidence.
4. Studies unrelated to psychological stress, anxiety, or the MGBA.
5. Studies focusing exclusively on gastrointestinal disorders without a relevant brain, stress, or anxiety-related outcome.
6. Studies in which microbiota-related findings were incidental and did not directly address the review question.
7. Duplicate publications.
8. Non-English publications for which a reliable full-text English version was unavailable.
9. Publications for which the full text could not be adequately assessed.

2.5 Study Selection

Search results retrieved from the respective databases were exported to a reference-management software program, and duplicate records were removed prior to screening. Titles and abstracts were initially screened according to the predefined eligibility criteria. Articles considered potentially relevant were subsequently subjected to full-text assessment.

The study-selection process followed the sequence:

Identification → Duplicate removal → Title and abstract screening → Full-text assessment → Final inclusion

The literature-selection process was documented by recording the number of records identified, duplicates removed, records screened, full-text articles assessed, and publications ultimately included in the final narrative synthesis.

As the present manuscript was designed as a structured narrative review rather than a systematic review, the study-selection flow diagram was intended to provide transparency regarding the search and selection process. It was not considered evidence of PRISMA-compliant systematic-review methodology unless all relevant PRISMA methodological requirements had been fulfilled.

2.6 Data Extraction

Data from eligible publications were extracted using a standardized data-extraction framework. Where applicable, the following information was recorded:

- First author and year of publication;
- Country or geographical setting;
- Study design;
- Human or experimental model;
- Sample size;
- Participant characteristics;
- Stress or anxiety phenotype;
- Microbiome assessment methodology;
- Principal microbial findings;
- Microbial metabolites investigated;
- Biological pathway investigated;
- Intervention and microbial strain, where applicable;
- Intervention dose and duration;
- Psychological outcome measures;
- Biological outcomes;
- Principal findings;
- Major methodological limitations; and
- Reported conflicts of interest and funding sources, where relevant.

For clinical intervention studies, particular attention was given to the specific microbial strain, formulation, dosage, intervention duration, and validated psychological outcome measures, as the effects observed with one probiotic strain or formulation cannot necessarily be generalized to other strains or preparations.

2.7 Evidence Organization and Synthesis

Given the substantial methodological and clinical heterogeneity among the available studies, the findings were synthesized narratively rather than through statistical pooling.

The available evidence was organized into six principal domains:

1. Neuroendocrine mechanisms: interactions between gut microbiota, the HPA axis, and stress-related hormones.
2. Neural mechanisms: vagal, enteric, and neuroepithelial signalling pathways.
3. Barrier and immune mechanisms: intestinal permeability, blood–brain barrier integrity, and immune or neuroinflammatory pathways.
4. Microbial metabolites: short-chain fatty acids, tryptophan-derived metabolites, and other neuroactive microbial products.
5. Clinical associations: relationships between gut microbial characteristics and psychological stress or anxiety in human populations.
6. Therapeutic interventions: evidence concerning probiotics, prebiotics, synbiotics, postbiotics, and other microbiota-targeted strategies.

Human and experimental evidence were interpreted separately wherever possible. Mechanistic findings derived from animal models were not considered direct evidence of clinical efficacy in human populations.

2.8 Assessment of Evidence Strength

The strength and translational relevance of the available evidence were considered according to study design, methodological quality, consistency of findings, and convergence across different evidence types.

Evidence was broadly categorized as follows:

- Stronger evidence: replicated human randomized controlled trials, systematic reviews or meta-analyses, and convergent findings across multiple study designs.
- Moderate evidence: consistent findings from observational human studies or limited clinical trials supported by relevant mechanistic evidence.
- Preliminary evidence: findings derived primarily from individual studies, small clinical samples, or experimental animal models.

This framework was used to distinguish established associations from mechanistic hypotheses and emerging therapeutic possibilities.

2.9 Critical Appraisal and Interpretation

Attention was given to potential confounding factors and methodological variables that may influence the interpretation of associations between gut microbiota and anxiety or stress. These included:

- Dietary intake;
- Age;
- Sex;
- Geographical location;
- Medication exposure;
- Antibiotic use;
- Physical activity;
- Sleep;
- Body composition and metabolic status;
- Baseline microbiome composition;
- Sequencing and bioinformatic methodologies; and
- Differences in instruments used to assess anxiety and psychological stress.

The potential influence of psychotropic medication was considered particularly important because medication exposure may independently modify gut microbial composition and function.

Accordingly, interpretation of microbiota-related findings emphasized the distinction between observed associations, biologically plausible mechanisms, and demonstrated causality.

2.10 Ethical Considerations

As the present review utilized previously published and publicly available scientific literature and did not involve the recruitment of human participants or collection of identifiable participant-level data, institutional ethical approval was not required.

2.11 Reporting Considerations

The review was prepared with an emphasis on transparent reporting of the literature-search strategy, eligibility criteria, evidence-synthesis procedures, and methodological limitations. Where applicable, established recommendations for narrative-review reporting were considered to enhance the quality, reproducibility, and transparency of the review process.

3. RESULTS

3. Results and Evidence Synthesis

3.1 The Microbiota–Gut–Brain Axis as a Bidirectional Communication Network

The contemporary understanding of the microbiota–gut–brain axis (MGBA) encompasses a complex network of interconnected physiological systems rather than a single communication pathway. Major components include the intestinal microbiota, enteric nervous system, autonomic nervous system, hypothalamic–pituitary–adrenal (HPA) axis, immune system, intestinal epithelium, blood–brain barrier and circulating microbial metabolites.[13]

The gut microbiota can influence host physiology through microbial metabolites, structural microbial components, and modulation of host signalling pathways. Conversely, central nervous system activity regulates gastrointestinal physiology through sympathetic and parasympathetic pathways, stress hormones, gastrointestinal motility, and behavioural factors such as dietary intake and sleep.

This bidirectional interaction is particularly relevant to psychological stress and anxiety. Sustained psychological stress may induce alterations in dietary behaviour, sleep patterns, intestinal motility, and autonomic activity before measurable changes in microbial composition become evident. Conversely, microbial metabolites and inflammatory mediators may influence neural circuits involved in emotional processing, reward, interoception, and stress responsiveness. Therefore, microbial alterations observed in individuals with anxiety may represent a cause, consequence, or intermediary component of the underlying condition.

Recent research has consequently shifted from static characterization of microbial composition toward assessment of microbial function. Approaches such as metagenomics, metabolomics, transcriptomics, and quantitative microbiome profiling may provide greater biological insight than relative microbial abundance alone.[9]

3.2 Psychological Stress and the Hypothalamic–Pituitary–Adrenal Axis

The **hypothalamic–pituitary–adrenal (HPA) axis** represents one of the principal biological systems linking psychological stress with gastrointestinal physiology. Perceived stress activates hypothalamic secretion of corticotropin-releasing hormone, followed by pituitary release of adrenocorticotropic hormone and subsequent secretion of glucocorticoids from the adrenal cortex. Cortisol and related glucocorticoids regulate multiple physiological processes, including metabolism, immune function, vascular activity, and gastrointestinal physiology.

The gut microbiota interacts bidirectionally with the HPA axis. Experimental evidence indicates that

alterations in the gut microbiota may influence stress responsiveness, whereas psychological stress can modify microbial composition and intestinal function. [4–6] This relationship is not necessarily linear, as comparable stress exposures may produce different microbial and behavioural responses among individuals. Such variability may reflect differences in host genetics, dietary patterns, previous environmental exposures, and baseline microbial ecology.

Persistent HPA-axis activation may also influence intestinal epithelial barrier function. Increased glucocorticoid and catecholamine signalling can modify gastrointestinal motility, secretion, and immune activity, thereby altering the ecological conditions within which microbial communities are maintained.

These observations suggest that microbiota-targeted interventions should not be considered independently of the broader stress-regulatory system. Persistent psychological stress, inadequate sleep, poor dietary patterns, or chronic inflammatory states may influence the durability and magnitude of microbiota-directed interventions.

3.3 Psychological Stress, Manasika Doṣa, and Agni–Dhatvagni in the Microbiota–Gut–Brain Axis

From an Ayurvedic perspective, the relationship between psychological stress and gastrointestinal physiology may be interpreted through the interconnected concepts of Manas, Manasika Doṣa, Agni, Āhāra-pāka, and Dhatvagni. Ayurveda describes Rajas and Tamas as the two Manasika Doṣas, whereas Sattva represents a relatively balanced mental state.[26] Psychological states such as Chinta (worry), Śoka (grief), Bhaya (fear), and Krodha (anger) are described in classical Ayurvedic literature as factors relevant to psychological health, disease processes, and digestion.[27,28]

A particularly relevant classical observation is that food may not undergo appropriate digestion when consumed during psychological states such as Chinta, Śoka, Bhaya, and Krodha.[27,28] This provides a classical framework for considering psychological state as a potential modifier of digestive function. Although the classical concept of Agni cannot be directly reduced to a single contemporary physiological parameter, this Ayurvedic perspective can be considered alongside modern evidence demonstrating that psychological stress influences gastrointestinal motility, secretion, intestinal barrier integrity, immune activity, and gut microbial ecology.[4-7,29]

Within Ayurvedic physiology, Jatharagni represents the principal transformative principle responsible for digestion and processing of ingested food. Classical Ayurvedic physiology further describes seven Dhatvagni, associated with Rasa, Rakta, Mamsa, Meda, Asthi, Majjā, and Sukra Dhatu.[30]These Dhatvagni are described as participating in the transformation and utilization of nutritional material relevant to their respective Dhatus.[30]

Accordingly, a conceptual Ayurvedic pathway may be proposed:

Psychological stress → predominance of Rajas/Tamas and mental disturbance → Chintā/Śoka/Bhaya/Krodha → disturbance of Jatharagni → altered

4.1 From the "gut microbiome" to the "gut ecosystem"

The evidence reviewed here supports a fundamental conceptual shift. It is increasingly inadequate to ask whether a particular bacterial genus is "good" or "bad" for anxiety. The clinically relevant question is whether microbial communities generate functional outputs that influence host physiology under specific environmental conditions.

Microbial diversity alone is not synonymous with health. A microbial community should instead be considered in terms of functional capacity, metabolic activity, resilience, and interaction with the host.

This perspective also explains why apparently contradictory findings can occur across studies. Different cohorts may possess distinct baseline microbiomes but similar metabolic functions. Conversely, similar microbial taxa may behave differently under different dietary or inflammatory environments.

4.2 Causation versus correlation

One of the most important unresolved questions is whether gut microbiota alterations cause anxiety or simply reflect anxiety-associated behaviours and physiology.

Three possibilities should be considered.

First, microbiota changes may contribute causally to anxiety through immune, endocrine, neural, or metabolic pathways.

Second, anxiety and chronic stress may alter the microbiome through HPA-axis activation, autonomic changes, diet, sleep disruption, and gastrointestinal motility.

Third, both microbiome and anxiety may be influenced by a common third factor such as medication, diet, socioeconomic conditions, metabolic disease, or early-life adversity.

The available evidence supports all three possibilities to some degree. The recent *Nature Mental Health* review explicitly emphasized this causal–correlative–bidirectional framework.[9]

Therefore, longitudinal studies are essential. Cross-sectional stool sampling cannot establish temporal direction.

4.3 Stress resilience as a major research target

Not everyone exposed to chronic stress develops an anxiety disorder. This phenomenon suggests that resilience may be more informative than disease status alone.

Microbial resilience—the capacity of an ecosystem to maintain or restore functional stability following perturbation—may potentially interact with psychological resilience.[4,6]

The 2024 *Cell* study is particularly relevant because it demonstrates how stress-sensitive brain circuitry can modify a specific intestinal microbial niche. [7] This raises the possibility that resilience is partly mediated by the capacity of brain–gut circuits to maintain mucosal homeostasis during stress.

Future studies should therefore examine individuals before, during and after major stress exposure rather than sampling only patients after anxiety have developed.

4.4 Why probiotic studies produce inconsistent findings.

Several factors can explain inconsistent clinical results.

Strain specificity

Different bacterial strains belonging to the same species may have distinct genomes, metabolic capabilities, and host interactions.

Baseline microbiome

A probiotic may produce different effects in individuals whose resident microbiota differs substantially.

Psychological phenotype

A healthy person with mild stress may respond differently from an individual with clinically diagnosed generalized anxiety disorder.

Lifestyle

Diet, exercise and sleep can independently influence both anxiety and microbial composition.[13]

Duration

Microbiome changes may require sustained exposure, whereas psychological effects may appear earlier or later.

Outcome selection

Anxiety is multidimensional. State anxiety, trait anxiety, generalized anxiety symptoms and stress perception are not interchangeable outcomes.

Medication

Psychotropic medications can themselves modify microbial profiles, creating substantial confounding.[22]
These considerations suggest that future psych biotic trials should adopt precision-medicine principles rather than testing broad “probiotic” categories.

4.5 Clinical implications

At present, microbiota-targeted interventions should be regarded as potential adjunctive strategies rather than replacements for established evidence-based management of anxiety disorders.

Psychological therapies, appropriate pharmacotherapy, physical activity, sleep optimization, and dietary improvement remain important components of comprehensive management. Microbiome-directed approaches may eventually complement these interventions by targeting biological pathways that differ among individuals.

A clinically useful future model could involve:

Patient phenotype → dietary assessment → medication assessment → microbiome/metabolome profiling → individualized intervention → longitudinal monitoring.

Such an approach would move the field from generic probiotic supplementation toward precision microbiome medicine.

4.6 Research priorities

Several priorities emerge from the current evidence.

1. Longitudinal human cohorts

Participants should be evaluated before, during and after naturally occurring stressors.

2. Standardized microbiome methodology

Studies should report sequencing platforms, depth, bioinformatic pipelines, dietary intake, and medication exposure transparently.

3. Functional rather than purely taxonomic analysis

Metagenomics and metabolomics should accompany 16S rRNA profiling whenever feasible.

4. Strain-resolved intervention studies

Psych biotic trials should identify strains at appropriate genomic resolution and report viable counts, formulation, and dose.

5. Mechanistic biomarkers

Cortisol, inflammatory markers, intestinal permeability, SCFAs, bile acids and tryptophan metabolites may provide
mechanistic endpoints.

6. Sex-specific analyses

Sex-related differences in anxiety prevalence, hormonal biology, diet, and microbial composition warrant dedicated analyses.

7. Medication-aware study design
Antidepressants, anxiolytics, proton-pump inhibitors, antibiotics, and other microbiome-active drugs should be carefully recorded.

8. Multi-omics integration
The future of MGBA research will depend on integration of metagenomics, metabolomics, transcriptomics, host genetics, and neuroimaging.

9. Replication across populations
Most microbiome research remains disproportionately concentrated geographical and socioeconomic populations. Cross-cultural replication is essential.

4.7 Dhatvagni as a conceptual extension of the microbiota–gut–brain model
The Ayurvedic concept of Dhatvagni provides a theoretical extension of the Agni model from primary gastrointestinal digestion to tissue-level transformation. Classical Ayurvedic physiology describes seven Dhatvagni corresponding to the seven Dhatus and attributes to them the transformation of nutritional material relevant to tissue nourishment.[30]

Contemporary microbiome research demonstrates that food-derived substrates are transformed by intestinal microorganisms into numerous bioactive metabolites. These metabolites can influence epithelial, metabolic, immune, endocrine and neural processes.[9,29] This provides a conceptual point of comparison with Dhatvagni, but Dhātvagni should not be identified with microbial metabolism, digestive enzymes, mitochondria or any single modern biochemical pathway. The appropriate scientific approach is to investigate whether measurable biological processes associated with nutrient transformation correlate with Ayurvedic assessments of Dhatvagni rather than assuming equivalence.

Psychological stress may be hypothesized to influence this process primarily through its effects on Jatharagni. Chronic stress can alter gastrointestinal motility, epithelial barrier function, immune signalling, food intake and microbial ecology.[4-7,29] These changes may modify the intestinal environment and availability of substrates for microbial metabolism. Conversely, microbial metabolites and immune or neural signals can influence brain function and stress responsiveness.[6,7,29]

The proposed integrative pathway is therefore: Manasika stress → Rajas/Tamas-related mental disturbance → Jatharagni disturbance → altered Āhāra-pāka → altered nutritional substrate → possible downstream influence on Dhatvagni-dependent transformation → Dhātu-puṣṭi, with reciprocal gut microbiota → microbial metabolites → immune/endocrine/neural signalling → brain/Manas → stress responsiveness. This is a hypothesis-generating framework rather than an established causal pathway.

5. Limitations
This review has several limitations. First, it is a narrative rather than a formal systematic review and therefore does not provide a quantitative risk-of-bias assessment for every included study. Second, microbiome methodology continues to evolve, making direct comparison between older and newer studies difficult. Third, much mechanistic evidence continues to originate from animal models, where controlled manipulation is possible but direct translation to human anxiety is uncertain. Fourth, substantial heterogeneity exists in anxiety definitions, psychological scales, microbiome sequencing approaches, and intervention formulations.

Another important limitation is publication bias.

Positive psych biotic findings may be more likely to receive attention than neutral or negative results. Recent systematic reviews nevertheless demonstrate that clinical evidence remains mixed, emphasizing the need for larger, well-controlled trials.[11,14]

6. CONCLUSIONS
The microbiota–gut–brain axis has developed from a conceptual framework into a biologically supported network involving neural, endocrine, immune, epithelial, and metabolic communication. Current evidence indicates that psychological stress can influence intestinal microbial ecology, while microbial signals can modulate physiological pathways relevant to stress responsiveness and anxiety.

The strongest contemporary advances concern mechanisms rather than simple microbial associations. Vagal communication, intestinal and brain barriers, immune signalling, SCFAs, tryptophan metabolism and microbial neuroactive compounds provide multiple potential routes through which the gut and brain interact. Experimental evidence has further demonstrated that stress-sensitive brain circuits can directly influence microbial niches within the intestine.[7]

However, the field should resist reductionist interpretations. There is no single microbial signature that currently defines anxiety, and the causal relationship between microbiome alterations and psychiatric symptoms remain incompletely established. Medication, diet, sleep, lifestyle, sex, age, and geography can all substantially modify the microbiome.

Clinical trials of probiotics and related interventions provide encouraging but inconsistent findings. Meta-analyses suggest that some probiotic and symbiotic interventions can improve anxiety-related outcomes, while other well-controlled trials have found no significant overall benefit.[11-14] These discrepancies indicate that microbial interventions are likely to be strain-, dose-, host- and context-dependent.

The next phase of MGBA research should therefore move beyond the question of whether the microbiome is associated with anxiety and instead determine which microbial functions influence which biological pathways, in which individuals, under which environmental conditions. Longitudinal multi-omics studies and mechanism-based randomized clinical trials will be central to answering this question.

Microbiome science may contribute to a more individualized understanding of stress and anxiety, particularly by identifying biological subtypes and developing adjunctive interventions. At present, however, the evidence supports the MGBA as promising research and therapeutic framework rather than an established standalone treatment for anxiety.

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