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Next-Generation Nutraceuticals Targeting the Gut–Brain Axis: Mechanisms and Clinical Evidence

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ABSTRACT: The gut–brain axis has emerged as a key regulator of neurological and mental health, yet nutraceutical research in this field remains dominated by probiotics, while a broader range of diet-derived bioactive compounds that modulate gut–brain communication without live microbes receives far less attention. This integrative review synthesizes mechanistic and clinical evidence on non-viable, metabolite-driven nutraceutical strategies, including postbiotics, microbially transformed phytochemicals, and dietary metabolites that interact with immune, neurological, and endocrine signaling. We describe how short-chain fatty acids, indole derivatives, phenolic metabolites, and bile acid-related compounds influence neurotransmitter synthesis, neuroinflammation, hypothalamic–pituitary–adrenal axis activity, and blood–brain barrier integrity, and we integrate findings from cellular, animal, and human studies to identify host receptors, signaling cascades, and context-dependent effects shaped by host physiology and microbiome composition. Interindividual variability, a major source of inconsistent intervention outcomes, receives particular attention. Rather than cataloguing compounds, we appraise the strength, limitations, and translational significance of the available evidence, identify methodological gaps in current intervention studies, and argue that reframing gut–brain nutraceuticals as modulators of microbe–host metabolic signaling, rather than microbial replacement therapy, provides a more precise and clinically actionable paradigm. We conclude by outlining research priorities, including biomarker-driven participant stratification, dose and duration optimization, and disease-specific outcome selection, to guide the rational development of next-generation nutraceutical therapies targeting the gut–brain axis.

1. INTRODUCTION

Expansion of the gut–brain axis concept in neurological and psychiatric research

The gut–brain axis has evolved over the last ten years from being solely a neuroanatomical idea to an expanded biological framework that connects brain activity and mental health with gastrointestinal function. It is now accepted as a multifaceted system which includes inflammatory pathways, microbial metabolites, endocrine control, and immunological signaling, rather than being limited to direct neural communication via the vagus nerve (Chen et al., 2022). Changes in gut microbiota composition have been connected to changes in the functioning of the central nervous system via mechanisms such as cytokine signaling, hypothalamic–pituitary–adrenal axis regulation, and how they influence neurotransmitter availability (Chen et al., 2022; Toader et al., 2024). In neurological and psychiatric research, where disruptions in gut–brain communication have been associated with illnesses including epilepsy, Parkinson's disease, autism spectrum disorders, depression, and anxiety disorders, this enlarged viewpoint has grown in significance (Chen et al., 2022; Toader et al., 2024; Cryan et al., 2019). Furthermore, recent research indicates that impaired cognition, emotional control, and stress responsiveness may be caused by immune system imbalance and low-grade inflammation that originates in the gut (Toader et al., 2024; Cryan et al., 2019). These results collectively offer fresh understanding of the molecular foundations of neuropsychiatric illnesses by supporting a unified

paradigm that posits a strong relationship amongst gut microbiota, immunological processes, and brain function.

Limitations of probiotic-centered nutraceutical strategies

Probiotics and related nutraceuticals have attracted interest as potential gut-brain axis modulators, but their safe application in neurological and psychiatric settings is hindered by a number of issues. Just a small percentage of probiotic formulations have been found to substantially enhance mood, anxiety, or cognitive symptoms in clinical investigations, and many trials have had inconsistent results or inadequate numbers of samples (Çimse et al., 2024; Mörtl et al., 2020). Inconsistent reactions across participants might result from the great degree of variation in individual microbiota composition, which influences how effectively probiotic cultures survive, colonize, and interact with indigenous microorganisms (Çimse et al., 2024; Wiegers et al., 2022). Furthermore, it makes it difficult to evaluate outcomes or standardize recommendations due to significant variations in strain selection, dosage regimens, and treatment durations among studies (Çimse et al., 2024; Mörtl et al., 2020). There are concerns concerning the long-term therapeutic significance of many probiotics since they only cause temporary, rather than permanent, modifications to microbial populations (Çimse et al., 2024). Aside from these practical obstacles, there are gaps in our knowledge of how probiotics can alter processes in the central nervous system, such as immune regulation, neurotransmitter synthesis, and barrier integrity, making it difficult to design treatments for specific disease conditions (Mörtl et al., 2020; Wiegers et al., 2022). For probiotic-centered nutraceutical remedies to be broadly recommended for neurological or psychiatric therapy, these constraints highlight the need for well-controlled, larger-scale trials, mechanistic research, and tailored approaches.

Rationale for focusing on non-viable, metabolite-driven interventions

Growing awareness of the drawbacks of live probiotic formulations has led to interest in non-viable, metabolite-driven therapies as alternatives for gut-brain axis modulation. Postbiotics, also known as non-viable microbial products, are a broad category of bioactive compounds that can affect host physiology without necessitating microbial viability or colonization. These include short-chain fatty acids, microbial peptides, cell wall components, extracellular vesicles, and other metabolites (Salminen et al., 2021; Aguilar-Toalá et al., 2018; Żółkiewicz et al., 2020). These elements have been shown to influence neuroactive and inflammatory signaling, improve intestinal barrier function, and interact with host immune pathways in ways that are frequently more predictable than live microbial administration (Salminen et al., 2021; Silva et al., 2020). Metabolite-based therapies, as compared to probiotics, are less reliant on host-specific factors such as dietary habits, gastrointestinal transit, or baseline microbiome composition, which may lessen therapeutic response variability (Żółkiewicz et al., 2020; Daliri and Lee, 2015). From a translational standpoint, non-viable formulations also have benefits in terms of safety, dosage consistency, and shelf stability, especially for populations who are neurologically or immunocompromised (Salminen et al., 2021; Taverniti and Guglielmetti, 2011). All of these variables point to a move in neurological and psychiatric research toward metabolite-focused approaches as a more controlled and mechanistically based way to target gut-brain communication.

Scope, objectives, and novelty of the review

The primary focus of this review is on nutraceutical strategies that affect the gut-brain axis without using live probiotic organisms. Its scope includes non-viable, metabolite-driven methods such as postbiotics and other substances produced from microbes that interact with metabolic, immunologic, and neuroendocrine pathways that are involved with interaction between the gut and the brain. Incorporating results from neurological, psychiatric, and gastrointestinal studies, the review integrates material that is sometimes seen in silos into a solid, integrated framework.

Examining the biological underpinnings and possible applications of these non-viable, metabolite-driven interventions is the primary goal, with a particular emphasis on how they vary from conventional probiotic-based approaches. In addition to highlighting sources of variability and limitations in previous studies, the review assesses current understanding of underlying processes and considers safety, formulation, and reproducibility concerns into account. By doing this, it aims to identify areas in which nutraceuticals centered on metabolite can have more reliable or controllable impacts on gut-brain signaling.

2. LITERATURE SEARCH STRATEGY

This article is a narrative (integrative) review. Because narrative reviews are susceptible to selection bias, we followed a structured, transparent search and selection process aligned with the SANRA guidance for narrative review articles. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for English-language articles published up to December 2025, with emphasis on literature from 2010 onward. Search strings combined controlled vocabulary and free-text

terms covering six concept blocks: (i) "gut-brain axis" OR "microbiota-gut-brain communication"; (ii) "nutraceutical" OR "functional food" OR "bioactive compound"; (iii) "postbiotic" OR "paraprobiotic" OR "non-viable" OR "cell-free supernatant"; (iv) "short-chain fatty acid" OR "indole" OR "bile acid" OR "polyphenol" OR "urolithin*" OR "lignan"; (v) "neuroinflammation" OR "neurotransmitter" OR "HPA axis" OR "blood-brain barrier"; and (vi) "clinical trial" OR "randomized" OR "intervention" OR "human". Reference lists of key reviews and consensus documents were screened for additional relevant sources (citation chaining). In vitro and animal studies were included when they described molecular mechanisms directly relevant to human gut-brain signaling; studies were excluded when they (a) focused exclusively on live probiotic interventions without a metabolite-related mechanistic component, (b) lacked a clear link between a dietary or microbial metabolite and a neurological or psychiatric endpoint, or (c) were non-peer-reviewed opinion pieces. Titles, abstracts, and full texts were screened sequentially by the authors, and the final reference set was verified individually for bibliographic accuracy (including DOI resolution) and for support of the specific statements for which each source is cited. Given the narrative design, no formal meta-analysis was performed; the certainty of evidence is appraised narratively in Sections 8 and 9.

3. THE GUT–BRAIN AXIS AS A METABOLIC AND SIGNALING NETWORK

It is becoming increasingly recognized that the gut-brain axis is not a simple communication channel between the central nervous system and the gastrointestinal tract, but rather a complicated metabolic and signaling network. Together, these neuronal, immunological, endocrine, and metabolic signals control behavior, stress response, and brain function. Bidirectional communication permits peripheral signals from the colon to influence brain processes involved in mood, autonomic regulation, and cognition, whereas central nervous system activity influences gut physiology (Torres-Fuentes et al., 2017; Carabotti et al., 2016).

Cytokines and inflammatory mediators control immune-mediated communication, which can enter the brain directly or indirectly via humoral pathways, whereas neural pathways, particularly those involving the vagus nerve and enteric nervous system, provide rapid signal transmission between the gut and brain (Torres-Fuentes et al., 2017; Rhee et al., 2009). Endocrine signaling also plays a role via gut-derived hormones and stress-related pathways, such as the hypothalamic-pituitary-adrenal axis, which links psychological stress to changes in gut permeability, immunological activity, and microbial composition (Carabotti et al., 2016; Foster and McVey Neufeld, 2013). In addition to these systems, metabolic communication has become an essential component of gut-brain transmission, making microbial metabolites essential bridges between host neurology and intestinal microorganisms.

Gut–brain interactions are primarily determined by microbial metabolites, including short-chain fatty acids, bile acid derivatives, indole compounds, and neurotransmitters generated by microbes (Moțățăianu et al., 2023; Silva et al., 2020). Either locally inside the enteric nervous system or systemically after entering circulation, these metabolites influence the integrity of the intestinal barrier, control immune cell activity, and affect neuronal signaling (Moțățăianu et al., 2023). Particularly, short-chain fatty acids have been shown to influence synaptic plasticity, neuroinflammation, and microglial maturation, underscoring their significance for brain development and function (Silva et al., 2020; Erny et al., 2015). By these means, microbial metabolites serve as active signaling molecules that have the ability to influence host physiology and behavior rather than being merely digested waste.

Crucially, one important factor influencing gut-brain results is host response. Neural response to microbial and metabolic signals are influenced by a number of variables such as basal metabolic state, immunological status, receptor expression, and genetic background (Rhee et al., 2009; Strandwitz, 2018). Divergent neurological or psychiatric outcomes across people may result from the same metabolite exposures or microbial profiles, which can be explained by variations in host sensitivity. This host-dependent modulation underlines that the gut-brain axis should not be seen as a homogeneous or deterministic system, but rather as a dynamic, context-sensitive network whereby microbial signals interact with host biology to affect brain function (Figure 1), (Table 1).

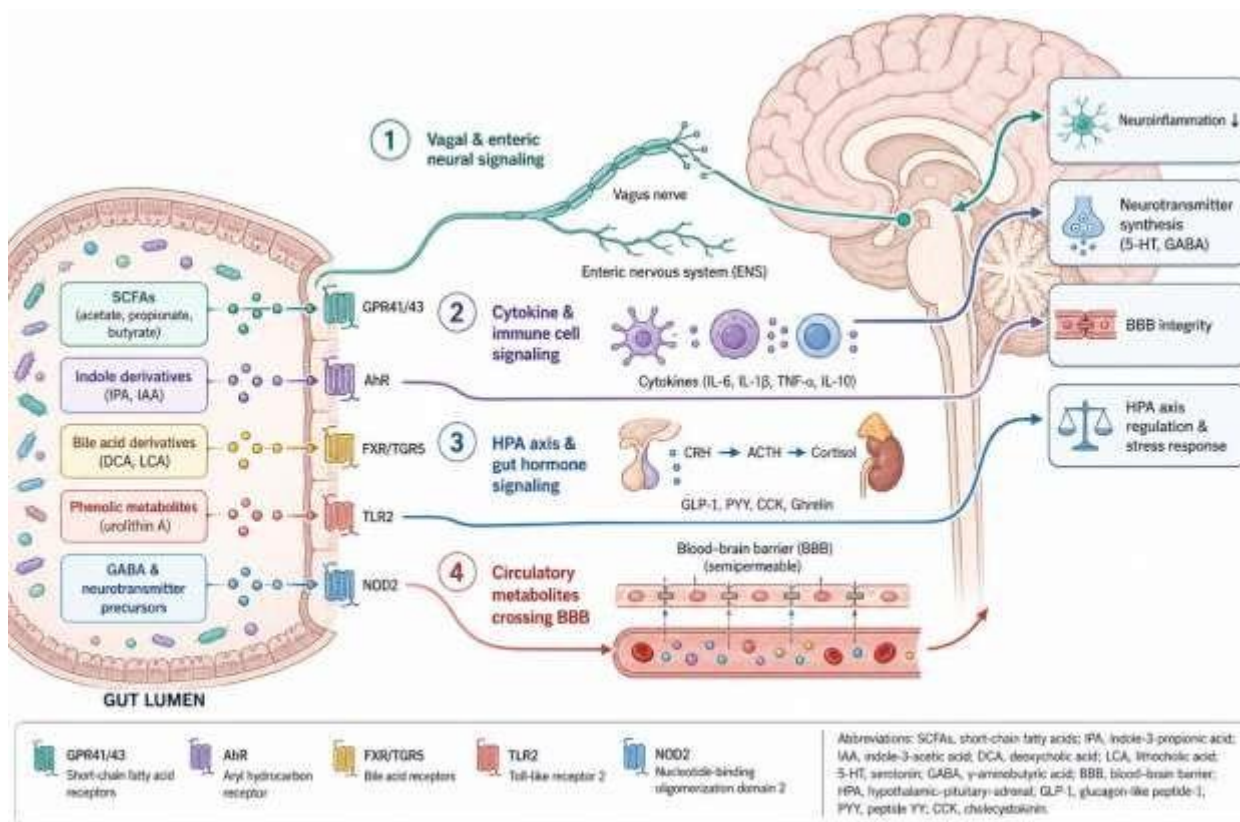


Figure 1. The gut–brain axis as a metabolic and signaling network. Gut-derived bioactive compounds, including short-chain fatty acids, indole derivatives, bile acids, phenolic metabolites, and neurotransmitter precursors, engage host receptors (GPR41/43, AhR, FXR/TGR5, TLR2, and NOD2) to modulate vagal and enteric neural signaling, cytokine and immune cell signaling, the HPA axis, and circulatory metabolites crossing the blood–brain barrier, thereby influencing neuroinflammation, neurotransmitter synthesis, barrier integrity, and stress responses.

4. POSTBIOTICS AS FUNCTIONAL NEUROACTIVE NUTRACEUTICALS

Recent advances in our understanding of the dynamics and activities of probiotics have led to a progressive transition in the use of live probiotic cultures to their not-living metabolic waste products, or postbiotics (Gurunathan et al., 2023). The term "postbiotic" precisely defines compounds that are produced after bacteria have expired, become inanimate, or become inactivated. A postbiotic's constituent microorganisms might be either dead, whole cells or structural pieces of bacteria, including cell wall of bacteria. A postbiotic must be synthesized from a specific bacterium or set of microorganisms whose genomic sequences are known and that are produced via a repeatable, technically defined process for biomass generation and inactivation (Gurunathan et al., 2023; Ozma et al., 2022). In Japan, postbiotics, which Mitsuoka dubbed "biogenics" in 1998, have been available for more than a century. In addition to new biotic nomenclature, it is important to draw attention to the most recent changes to the ISAPP consensus statement about the definition and application of postbiotics (Salminen et al., 2021). Postbiotics are defined by the ISAPP as [i] "[soluble factors secreted by live bacteria, or released after bacteria lysis, such as enzymes, peptides, teichoic acids, peptidoglycan-derived muropeptides, polysaccharides, cell-surface proteins, and organic acids"; [ii] "non-viable metabolites produced by microorganisms that exert biological effects on the hosts"; and [iii] "compounds produced by microorganisms, released from food components or microbial components, including non-viable cells that, once administered in adequate amounts, promote health and well-being." "Microbial peptides, indole derivatives, and short-chain fatty acids" (Gurunathan et al., 2023).

Food-grade microbes secrete postbiotics, or they are released following cell lysis in complex microbial cultures [cell-free supernatant], food, or the intestine (Amobonye et al., 2025; Liang and Xing, 2023). Following the supernatant's extraction, either the effects of the supernatant itself can be investigated or particular compounds may be separated for additional research. (Gao et al., 2019) The kind of bacterial strain, the growing medium, and the management of the bacteria following

multiplication are the primary factors influencing the quantity and type of postbiotic products (Gurunathan et al., 2023; Liang and Xing, 2023). Only soluble components, such as products or metabolic byproducts released into the medium during bacterial growth, are regarded as postbiotics in food that does not undergo any post-propagation treatment (Gurunathan et al., 2023; Liang and Xing, 2023). However, some studies employ cell fragmentation techniques such as thermal, enzyme-based, chemical, sonication, hyperbaric, solvent extraction, or a combination of these to lyse bacterial cells after they have been propagated (Gurunathan et al., 2023; González-González et al., 2020; Hernández-Granados and Franco-Robles, 2020; Żółkiewicz et al., 2020). In addition to adding several new intracellular metabolites and components produced by cell walls to the postbiotic mixture, these therapies provide the resulting postbiotics new functions (Gurunathan et al., 2023).

To distinguish the bacterial cells from the postbiotic metabolites, the outcomes underwent further extraction and purification processes, including centrifugation, dialysis, lyophilization, and column purification for the treated and untreated postbiotic combinations. (Amobonye et al., 2025; Liang and Xing, 2023; de Almada et al., 2016). Since each stage influences the final postbiotics' quantity and grade and yields different postbiotics with varying effects, postbiotics are frequently characterized by the microorganisms utilized as starting points and the inactivation processes or techniques used for their synthesis (Amobonye et al., 2025; Liang and Xing, 2023; Aggarwal et al., 2022).

A number of variables, such as the kind of microbe, its structural makeup, and its physiological roles, influence how postbiotics are categorized. It has also been determined that probiotic bacteria, both intracellular and extracellular, produce a variety of postbiotic compounds. Peptidoglycans, surface-extending molecules; exopolysaccharides [EPSs], teichoic acids, made up of cell wall components like fimbriae, pili, or flagella, secreted peptides and proteins bacterial substances like acidophilin, reuterin, and bifidin, cell-free extracellular fluids, organic acids, brain chemicals; and biosurfactants are all known to contain muropeptides (Gurunathan et al., 2023). Inactive and dead probiotics, peptidoglycans, teichoic acids, exopolysaccharides, cell-free residues, short-chain fatty acids, bacteriocins, enzymes, and vitamins are among the various postbiotic types that are grouped in accordance to their distinct physical, chemical, and functional characteristics (Gurunathan et al., 2023).

Inactivated and dead probiotics

Though other techniques like gamma or UV radiation, tyndallization, sonication, and chemical treatment can also be utilized (Ozma et al., 2022), heat is the method most commonly employed to create non-viable preparations. The inactivation process causes changes in the biological activities and cellular composition (Gurunathan et al., 2023). Experimental model studies demonstrated that the non-viable cells maintain the biological characteristics of their viable counterparts, such as reducing inflammatory indicators, scavenging oxygen radicals, and modifying host physiology. Eight strains of *Lactobacillus reuteri* were investigated; their heat-killed and live cells connected to caco2 cell culture and prevented enteropathogens such as *Salmonella typhi*, *E. coli*, *Listeria monocytogenes*, and *Enterococcus faecalis* from adhering (Gurunathan et al., 2023; Taverniti and Guglielmetti, 2011; Sugahara et al., 2017; Singh et al., 2017; Aggarwal et al., 2022).

Peptidoglycans

Specifically in *Lactobacillus* strains and other gram-positive probiotics (Amobonye et al., 2025), peptidoglycans, which are frequently made up of alternating N-acetylglucosamine [GlcNAc] and N-acetylmuramic acid [MurNAc] residues, are essential for the integrity, appearance, and stiffness of cell walls (Zheng et al., 2024). The bioactivities of these substances have also been studied; for instance, it has been demonstrated that the peptidoglycan from *Lactocasei bacillus rhamnosus* GG improves immune system responses and has anti-inflammatory properties (Salva et al., 2021).

Teichoic acids

The vast majority of Gram-positive bacteria contain teichoic acids, which are anionic polymers made of glycerol phosphate or ribitol phosphate, in their cell walls, capsules, and membranes (Balaguer et al., 2021). These substances, which are classified as derivatives of polysaccharides, have encouraging immunomodulatory qualities (Gurunathan et al., 2023; Liang and Xing, 2023). The two main kinds of teichoic acids are lipoteichoic acid and wall teichoic acid, which possess significant bioactivities in immunological modulation and gut colonization, particularly among *Lactobacillus* species (Amobonye et al., 2025; Liang and Xing, 2023; Bron et al., 2012; Sengupta et al., 2013). For instance, lipoteichoic acids in a postbiotic from *Lactobacillus rhamnosus* GG reduced inflammation and controlled immune responses in a mouse model of colitis; similarly, lipoteichoic acids from *Lactobacillus plantarum* have been shown to have anti-inflammatory properties on the human intestinal epithelial cells by preventing the production of interleukins (Amobonye et al., 2025; Liang and Xing, 2023; Noh et al., 2015).

Cell-Free Supernatants

Cell cultures can be used to produce cell-free excess fluid that contains biologically active metabolites that yeast and bacteria release into the surrounding liquid. After an incubation time, the bacteria are extracted by centrifugation. Finally, the mixture is filtered to ensure sterility. Cell-free supernatants [CFSs] are a large group of biomolecular and metabolically active molecules with low or high weights of molecules, such as organic acids, diacetylene, and carbon dioxide, and compounds that resemble bacteriocin and are typically released by lactic acid bacteria and yeasts (Gurunathan et al., 2023). These substances may aid in maintaining homeostasis in the body. A medium's composition may have an impact on the composition of CFS. Fluids known as cell-free supernatants [CFSs] include any leftover metabolites from microbial development as well as nutrients from the growth medium that are not taken by microorganisms. CFS, which develops when microorganisms ferment, is used to treat diarrhea and possesses antibiofilm, antibacterial, antioxidant, anti-inflammatory, and anticancer properties (Gurunathan et al., 2023). The unique compositional profile of cell-free supernatant [CFS] generated by lactic acid bacteria [LAB] is attracting increasing attention from researchers studying different macromolecules in search of health-promoting qualities. The CFS of LAB is made up of low molecular weight (such as, reuterin, hydrogen peroxide, carbon dioxide, organic acids, and di-acetylene) and high molecular weight (such as bacteriocins and molecules that resemble bacteriocins) chemicals together referred to as metabolites (Gurunathan et al., 2023; Mota et al., 2017). It has been established that the CFS from *Lactobacillus* contains anti-pathogenic qualities, such as anti-biofilm, antioxidant, and decreased NO activity (Liu et al., 2023). In addition to potentially reducing pigmentation, the CFS from *L. gasseri* BNR17 may help with menopausal symptoms, type 2 diabetes, managing your weight, and irritable bowel syndrome (Liu et al., 2023; Lee et al., 2022). In addition, the CFS from *Bacillus thuringiensis* and *Lactobacillus* has anti-biofilm properties (Liu et al., 2023; Sornsenee et al., 2021). The host immune system may be immunomodulated by CFSs. They can affect immune cell synthesis and function, particularly immunoglobulins, chemokines, and cytokines. By improving macrophage phagocytosis and upregulating pro-inflammatory cytokines, including interleukin-7 [IL-7] and tumor necrosis factor-alpha [TNF- α], the CFS from lactic acid bacteria [LAB] increases host immunological activity (Liu et al., 2023). CFSs may impact the host animal's overall gut health and function by modifying host-microbe interactions. CFS from *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, and *Lactobacillus reuteri* were discovered just recently to be able to block vaginal epithelial cell infections, which makes them a possible preventive tool for vaginal infections in cows (Liu et al., 2023; Lee et al., 2022; Spaggiari et al., 2022). Additionally, CFS treatment has been found to reduce oxidative stress and inflammation brought on by indomethacin in mice (Liu et al., 2023; Samer et al., 2022). The microbial makeup, growing circumstances, and experimental setting may all influence the unique roles of CFS (Liu et al., 2023).

Short Chain Fatty Acids [SCFAs]

Intestinal bacteria absorb plant polysaccharides to create SCFAs, a significant class of metabolites (Ozma et al., 2022; Kim et al., 2018). Acetic, propionic, and butyric acids [SCFAs] are produced by the gut bacteria fermenting food fibers. Butyrate is primarily generated by the commensal bacteria *Faecalis bacterium prausnitzii* and *Eubacterium rectale*, and its anti-inflammatory qualities have been shown (Ozma et al., 2022; Auger et al., 2022). Butyrate is metabolized from dietary fibers and has been shown to weaken both the LPS-induced $\text{I}\kappa\text{B}\alpha$ degradation/phosphorylation and NF- κB binding to DNA while enhancing histone H3 acetylation (Lee et al., 2017). Fermentation bacteria produce SCFAs, which have been recognized as critical molecules regulating neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease (Dalile et al., 2019). SCFAs also possess anti-inflammatory potential in vivo and mediate communication between the intestinal microbiome and the immune system. (Da et al., 2024)

Exopolysaccharides OR EPS

Exopolysaccharides are long-chain, high-molecular-weight polymers that are branching, repeating units of sugars or sugar derivatives and are mostly composed of lactic acid bacteria (Ozma et al., 2022). EPS can be divided into two groups based on their chemical composition: heteropolysaccharides, which have repeating units made up of multiple distinct monosaccharides (xanthan, gellan, galactan, and kefiran), and homopolysaccharides, which only contain one type of monosaccharide molecule (cellulose, levan, curdlan, pullulan, and dextran) (Ozma et al., 2022; Chaisuwan et al., 2020). EPS is frequently produced by lactic acid bacteria (LAB). The most common LABs that produce EPS are *Lactobacillus*, *Weissella*, *Leuconostoc*, *Lactococcus*, *Pediococcus*, *Streptococcus*, and *Bifidobacterium* species (Jurášková et al., 2022). An in vitro hydroxyl radical scavenging activity test revealed that Levan [S81], a HoP from *Leuconostoc mesenteroides* S81, had a strong immunomodulatory effect, induced the anti-inflammatory cytokine IL-4, and had an excellent antioxidant capacity with a half maximal effective concentration [EC50] value of 1.7 mg mL⁻¹. (Jurášková et al., 2022; Taylan et al., 2019). Using a hyaluronidase enzyme test,

Prado et al. investigated the anti-inflammatory properties of kefir polysaccharide extract [ExPP] and found that ExPP suppressed the hyaluronidase enzyme. Hyaluronic acid is hydrolyzed by the enzyme hyaluronidase, which breaks down the extracellular matrix and promotes inflammation. When compared to dimethyl sulfoxide, researchers found that lyophilized [L] ExPP had 63% anti-inflammatory effectiveness. (Jurášková et al., 2022; Prado et al., 2016)

It has been found that EPSs from LAB work as natural, potent antioxidants by helping to eliminate free radicals. Because of their toxicity, they have also been shown to be safe, indicating that they may be utilized in place of synthetic antioxidants (Jurášková et al., 2022; Rahbar Saadat et al., 2019).

Bacteriocins

Lactic acid [LAB] and other eubacteria and archaeobacteria create bacteriocins, a wide-ranging collection of over hundreds of ribosomal-manufactured short peptides or proteins that have the ability to either kill or stop the growth of other bacteria (De Vuyst and Leroy, 2007). Nisin, enterocin, subtilisin, bovicin, lactocyclin, lacticin, plantaricin, and lactococcin G&Q are a few examples. The potential of bacteriocins in food preservation is shown (Perez et al., 2014). Regulatory organizations such as the FDA, Health Canada, and the European Food Safety Authority [EFSA] authorized nisin as the first bacteriocin to be used commercially as a food preservative (Gurunathan et al., 2023; Ozma et al., 2022). More than 80 nations currently use it as a food ingredient. By limiting the creation of holes in cell membranes, impeding the normal building of cell walls, and obstructing the activity of proteins and enzymes, bacteriocins stop the spread of infections in the gastrointestinal tract (Gurunathan et al., 2023; Belguesmia et al., 2020).

Vitamins

Since humans lack the metabolic processes required for vitamin production, they must obtain their vitamins from external sources (Huskisson et al., 2007). These vitamins are necessary for a number of bodily functions, such as riboflavin's role as a hydrogen carrier in redox reactions, vitamin K's role as a cofactor of gamma carboxylase activity in blood clotting, bone health, and neurological functions, and folate's role in DNA replication, repair, and methylation (Huskisson et al., 2007; Hossain et al., 2022; Uebanso et al., 2020). commensal in the gut, especially lactic acid bacteria and *Bifidobacterium* sp. contain a number of B group vitamins, including vitamin K (Hossain et al., 2022) and nicotinic acid, riboflavin, cobalamin, pyridoxine, thymine, niacin, and folate (Gurunathan et al., 2023). Fermented foods like cheese, yogurt, and milk may contain large amounts of these vitamins. Vitamins generated by gut commensals are mostly digested in the colon, while dietary vitamins are primarily absorbed in the small intestine (Mota et al., 2017; Uebanso et al., 2020).

Signaling via receptors and subsequent neuronal consequences

Bacterial metabolites interact with the host for producing the beneficial effects of postbiotics (Ozma et al., 2022; Liu, 2025). Peptidoglycan, lipoteichoic acid, or LTA, exopolysaccharide, or EPS, S-layer protein A, or SlpA, and genomic DNA are examples of conserved microbe-associated molecular patterns [MAMP] found in *Lactobacillus* species. Pattern recognition receptors are able to recognize these patterns and initiate downstream signaling cascades that result in the advantageous actions. Different host interactions with probiotics and paraprobiotics are made possible via toll-like receptors with nucleotide-binding oligomerization domain-like receptors (Ozma et al., 2022; Bron et al., 2012; Teame et al., 2020; Sengupta et al., 2013; Furnari et al., 2025).

Toll-Like Receptors OR TLRs

Different MAMP families have been identified by Toll-like receptors. TLR9 reacts to unmethylated CpG oligonucleotide [CpG-ODN], TLR2 detects LTA and peptidoglycan, and TLR2/TLR4 detects bacterial EPS via RP105/DM1. Through TLR2, the *Lactobacillus reuteri* DSM 17938 strain protected necrotizing enterocolitis. *L. plantarum* LTA was recognized by TLR2, which also inhibited Pam2CSK4-induced IL-8 production (Ozma et al., 2022; Teame et al., 2020).

Nucleotide-binding Oligomerization Domain-Like Receptors, i.e., NLRs

NLRs are a large family of PRRs that may be divided into many sub-families depending on their N-terminal effector domains. Two well-researched NLR proteins are NOD1 and NOD2 (Ozma et al., 2022; Zhou et al., 2023). NOD2 is necessary for the regulation of the molecules' NAM-D-Ala-D-Glu unit, whereas NOD1 recognizes structures that comprise D-Glu-mDAP (Ozma et al., 2022). *Lactobacillus* mucopeptide recognition by NOD2 can have anti-inflammatory effects and protect animals against colitis. Numerous signaling molecules from *Lactobacillus* strains, including peptidoglycan components, were detected by

NODs; this sensing led to activation of NF- κ B and antibacterial activity (Ozma et al., 2022; Llewellyn and Foey, 2017; Warner et al., 2013).

C-Type Lectin-Like Receptors or CTLRs

CTLRs use one or more carbohydrate recognition domains [CRDs] to recognize carbohydrate molecules. CTLRs attach to sugar groups found in microbial peptidoglycan's glycan backbone. Certain CTLRs influence a spectrum of immune responses by activating or suppressing a wide range of signaling pathways through ligand binding (Ozma et al., 2022; Veldhuizen et al., 2011; Irazoki et al., 2019). A CLR called DC-specific ICAM-3-grabbing nonintegrin [DC-SIGN] is primarily expressed on dendritic cells [DCs] and is capable of identifying glycans that include fucose and mannose on the cell surfaces of several *Lactobacilli* bacteria. It has recently been shown that DC-SIGN joins *L. acidophilus* SlpA in vitro (Ozma et al., 2022; Gupta and Gupta, 2012). The Th1/Th2 ratio was lowered as a result of the SlpA-DC-SIGN interaction, which increased IL-10 release in DCs and encouraged the growth of T cells that generate a lot of IL-4. Additionally, it was found how SI-pA-induced protective immune modulation functions in vivo (Ozma et al., 2022; Konstantinov et al., 2008).

G-Protein-Coupled Receptors or GPCRs:

The most researched GPCRs are GPR41 and GPR43, which are expressed by adipocytes, epithelial cells, enteroendocrine cells, and sympathetic nervous system cells and are mainly triggered by short-chain fatty acids [SCFAs]. Butyrate and propionate, which are generated by gut bacteria and interact with GPR43, control the development of Foxp3⁺ Treg cells (Ozma et al., 2022; Dalile et al., 2019; Canfora et al., 2019). Additionally, it has been shown that GPR109A can detect SCFAs. For example, the butyrate-induced activity of the GPR109A receptor produced regulatory and IL-10-producing T cells, which improved anti-inflammatory characteristics in colonic macrophages and dendritic cells and lowered colon inflammation and carcinogenesis (Ozma et al., 2022; Parada Venegas et al., 2019; Singh et al., 2014). Furthermore, through GPCR signaling, SCFAs generated by gut bacteria may control glucose homeostasis, insulin tolerance, and lipid metabolism (Ozma et al., 2022; Teyani and Moniri, 2023).

5. MICROBIAL BIOTRANSFORMATION OF DIETARY PHYTOCHEMICALS

Gut microbiota as a metabolic gatekeeper

By turning dietary nutrients into bioactive natural products, the gut microbiota sheds light on how food and dietary supplements affect the well-being of individuals. The intricate relationship among gut microbiota, host metabolism, and dietary substrates emphasizes how crucial it is to comprehend those connections in order to control health and illness (Gojda and Cahova, 2021). In addition, the metabolism of other amino acids, including tyrosine, phenylalanine, and tryptophan, is significantly impacted by gut microorganisms. For example, the gut microbes *Bacteroides ovatus* and *Lactobacillus plantarum* may produce 4-ethylphenyl sulfate, i.e., 4EPS, from tyrosine, which may have an impact on brain function and behavior (Needham et al., 2022).

A few types of bacteria encountered in the colon have significance for metabolic signaling, the bacteria's breakdown of amino acids, and the synthesis of short-chain fatty acids (SCFAs), which are plentiful sources of energy for the host (Jandhyala, 2015). The predominant metabolic end products of the Firmicutes groups (*Lachnospiraceae*, *Ruminococcaceae*) are mostly butyrate, while *Bacteroidetes* create acetate and propionate. Butyrate is the most crucial element in the colon cell's energy metabolism, even though acetate and propionate serve as substrates for lipogenesis, glucose synthesis, and protein synthesis. The control of hepatic lipids and glucose homeostasis, including the effect of the receptors activated by PPAR on gluconeogenesis and lipogenesis, is greatly impacted by acetate, propionate, and butyrate (Gurunathan et al., 2023; Catinean et al., 2018). In addition, tryptophan is converted to active compounds by the gut microbes. For instance, *E. coli* manufactures indoles, which are crucial signaling molecules with primarily physiological functions (such as antibiotic resistance, biofilm formation, and motility) (Li and Young, 2013). The gut microbiota's direct and indirect means are well known for their potential pharmacokinetic effects, either by directly engaging in the metabolism of NPs or by indirectly interacting mechanistically with the host enzymatic system. The generation of microbial or mammalian microbial co-metabolites that compete for the metabolism of xenobiotic chemicals present in human food, including natural products, or function as signaling molecules that affect the host gene expression facilitates the indirect connection (Wikoff et al., 2009; Spanogiannopoulos et al., 2016).

Generation of brain-relevant metabolites from polyphenols and other bioactives

A vital component of the human diet is polyphenols. Fruit, vegetables, grains, seeds, beans, spices, herbs, oils, and all food items derived from these fundamental ingredients are from which we receive them. (Milovanovic et al., 2009). The largest amounts are usually ingested as alcoholic and nonalcoholic drinks, including tea and wine, fruit and fruit juices, and vegetables (Fraga et al., 2019).

Plant secondary metabolites termed dietary polyphenols, which have anti-inflammatory and antioxidant effects, often arrive in the small intestine attached to glycoside molecules and must be released in order to be absorbed (Diotaiuti et al., 2025). The majority of polyphenols avoid this process and reach the colon, where they could serve as bacterial substrates. Numerous mechanisms, including isomerization, dihydroxylation, ring fission, hydrolysis,

reduction, decarboxylation, and demethylation are involved in the microbial modification of polyphenols. Once in the bloodstream, phenolic compounds (PC) may travel to most organs, including the brain (Diotaiuti et al., 2025; Kumar Singh et al., 2019).

Flavonoids

The gut microbiome mostly transforms dietary flavonoids into phenolic acids. Almost all isoflavonoids, including genistin and daidzin, and their aglycones, genistein and daidzein, are found in soybeans and products derived from soy, such as tofu, soymilk, and miso soup. These products usually contain 0.01% to 0.3% isoflavonoids (Domínguez-López et al., 2024; Miadoková, 2009). After consumption, intestinal glucosidases break them down and absorb the resulting aglycones. The isoflavone daidzein gets broken down by intestinal bacteria using reductase enzymes to produce equol and O-desmethylangolensin (Mayo et al., 2019). Equol has been shown to enhance brain health through a number of different methods of action. Based on in vitro research, equol has neuroprotective qualities that prevent the cytotoxicity of β -amyloid plaques produced in a cellular model of Alzheimer's disease [AD] and promotes glial cell migration, a crucial phase for brain growth (Diotaiuti et al., 2025; Jamal et al., 2025).

Ellagitannins

Nuts and some fruits, such as pomegranates and berries, include ellagic acid and ellagitannins, which are often poorly absorbed (Diotaiuti et al., 2025). The gut bacteria in the intestinal system breaks down ellagitannins into ellagic acid, which is then hydrolyzed into urolithins. These compounds have potential uses as dietary indicators in addition to their health benefits (Espín et al., 2013; Raya-Morquecho et al., 2025). Animal studies have shown that urolithins are found in a variety of tissues, including the brain, which may suggest that they can cross the blood-brain barrier (Zhang et al., 2025). An in silico prediction of BBB permeability indicated that urolithin A & B and its methyl derivatives matched the theoretical conditions for BBB penetration (Diotaiuti et al., 2025; Zhang et al., 2025). In recent years, urolithin A has been shown to have promising impacts on neurocognitive health. Numerous preclinical and in vivo studies have shown that urolithin A is involved in a number of molecular processes that stop cognitive decline. It promotes neurogenesis, inhibits apoptosis, and lessens the development of β -amyloid plaques. Furthermore, urolithin A reduces the toxicity of β -amyloid plaques, attenuates tau hyperphosphorylation, and stimulates mitophagy, a clearance mechanism that is compromised in patients with Alzheimer's disease (Diotaiuti et al., 2025; Domínguez-López et al., 2024; Huang et al., 2025).

Lignans

The mammalian lignans enterodiol and enterolactone are produced in the colon by bacteria that are active on lignan plant precursors, including secoisolariciresinol diglycoside, which are prevalent in fiber-rich diets like grains and present in lower amounts in vegetables and fruits (Diotaiuti et al., 2025; Domínguez-López et al., 2024; Senizza et al., 2020). While dietary lignans have been linked to neurological benefits, nothing is known about the function of the metabolite enterolactone. Because it inhibits the generation of proinflammatory cytokines and nitric oxide in murine microglia, this enterolignan has shown neuroprotective qualities in in vitro experiments. (Diotaiuti et al., 2025; Senizza et al., 2020) Köse and Gulcin discovered that it can block the enzymes necessary for the development of AD, including carbonic anhydrase, acetylcholinesterase [AChE], and butyrylcholinesterase [BChE], in vitro (Köse and Gulcin, 2017). A few clinical and observational studies have found a significant correlation between dietary lignans and cognitive performance in human research (Diotaiuti et al., 2025; Ma et al., 2024).

Hydroxyphenylacetic, hydroxybenzoic, and hydroxycinnamic acids

The most common dietary sources of phenolic acids include nuts, whole grains, coffee, and fruits. The possibility of phenolic

acids penetrating the blood-brain barrier and entering the brain has produced results that are inconsistent. (Domínguez-López et al., 2024). Caffeic acid, a hydroxycinnamic acid, has been studied in both humans and animals to determine its permeability. Caffeic acid's presence in CSF may suggest that it can enter the bloodstream and go to brain cells. (Grabska-Kobylecka et al., 2020) Levels in CSF and plasma did not correlate, indicating that simple or facilitated diffusion is not the mechanism by which caffeic acid is carried across the blood-brain barrier.

Furthermore, the authors indicate that transitory conjugation or de-conjugation of polyphenols occurs in close proximity to the BBB and that conjugation processes may increase permeability (Diotaiuti et al., 2025; Domínguez-López et al., 2024). Caffeic acid's effects on cognition have been extensively studied. Caffeic acid has been shown through in vitro to suppress β -amyloid formation, reverse tau hyperphosphorylation, and restore dopaminergic neurotransmission to reduce oxidative damage (Diotaiuti et al., 2025; Caruso et al., 2022). According to some research, vanillic acid is a strong antioxidant that may inhibit AChE and BChE and lower nitric oxide, malonaldehyde, and the activities of oxidative stress-associated enzymes in hippocampus cells (Köse and Gulcin, 2017; Siddiqui et al., 2018). By promoting mitochondrial biogenesis and modifying the expression of genes involved in neural development, it may also have neuroprotective effects, according to in vitro studies (Diotaiuti et al., 2025; Augustyniak et al., 2018). Vanillic acid significantly boosted neurite development and decreased inflammatory molecule expression in hippocampus neurons with induced inflammation, as reported by Siddiqui et al. (Siddiqui et al., 2018). In vivo experimental models have demonstrated the positive effects of vanillic acid on the brain. Vanillic acid improved spatial learning and memory in mice with induced neurodegeneration and was linked to a reduction in inflammatory, cortisone, and AChE molecules (Diotaiuti et al., 2025; Singh et al., 2014). Vanillic acid lowered β -amyloid plaque formation, neuronal death, neuroinflammation, and oxidative stress in further studies using animal models of cognitive impairment (Domínguez-López et al., 2024).

Hydroxytyrosol

Many studies have shown that when hydroxytyrosol enters the brain, it has a neuroprotective impact (Terracina et al., 2022). It reduces the levels of MAO inhibition products associated with Parkinson's disease, according to in vitro research (Diotaiuti et al., 2025). Additionally, hydroxytyrosol helps prevent AD by stabilizing fibrils and oligomers, lowering oxidative stress, and preventing β -amyloid plaques from aggregating (Visioli et al., 2020). In a cellular model, hydroxytyrosol also reversed the mitochondrial energy deficit. Hydroxytyrosol can additionally assist with other neuroinflammatory diseases (Visioli et al., 2020). Research conducted on rats revealed that it decreases apoptosis and stimulates the production of anti-inflammatory molecules, which improves the results of stroke and neuropathic pain (Diotaiuti et al., 2025; Cao et al., 2023).

Modulation of Neuroinflammation Through Gut-Derived Signals

Several neurological conditions have a pathogenic mechanism that includes the process of neuroinflammation. Damage to the proximal brain parenchyma may occur from aberrant and uncontrollably activated glia, which is one of the harmful characteristics of neuroinflammation. Neuroinflammation is primarily caused by leukocyte response to protein aggregation and accumulation in the central nervous system, as well as a failure to differentiate self from non-self (Cao et al., 2023).

6. INFLUENCE OF NUTRACEUTICALS ON NEUROTRANSMITTER AND ENDOCRINE PATHWAYS

Serotonin signaling and tryptophan metabolism

A phylogenetically conserved signaling molecule with a range of functions in almost all living things is serotonin, additionally referred to as 5-hydroxytryptamine (5-HT). In animals, serotonin serves as a growth factor, a vasoactive agent, a local hormone in the gut, and a neurotransmitter in the central nervous system (CNS) (Kulkarni et al., 2022; Berger et al., 2009). The raphe nuclei were the primary source of serotonergic neurons in the central nervous system [CNS] that extend throughout the brain and affect important processes including mood, anxiety, appetite, sleep-wake cycles, cognition, learning, and memory (Ozma et al., 2022; Pourhamzeh et al., 2021). Enterochromaffin [EC] cells that line the gastrointestinal system produce and store a significant amount of the body's serotonin [$\sim 90\%$ – 95%] in the periphery (Rezzani et al., 2022). Gut-derived serotonin can play an essential function in controlling inflammation, sensation, intestinal fluid and mucus formation, and gut motility. (Guzel and Mirowska-Guzel, 2022).

A unique feature of serotonin synthesis is its reliance on the availability of its precursor, the crucial amino acid LTrp, which can only be obtained by diet (Ozma et al., 2022; Gasmi et al., 2022).

All creatures require tryptophan [Trp], an amino acid that is produced by bacteria, fungi, and plants and given to trophic layers above. In addition to being a part of protein synthesis, Trp is a required substrate for the production of several important bioactive substances. For instance, the pineal gland uses tryptophan as a substrate to produce melatonin, while the stomach and brain use it to produce serotonin (5-hydroxytryptamine, 5-HT). In vertebrates, central 5-HT affects the neuroendocrine and behavioral stress response (Barik, 2020; Keszthelyi et al., 2009).

After being synthesized and released, serotonin binds to a wide variety of different receptors in order to provide its wide range of effects. Based on their structural, pharmacological, and signaling characteristics, at least 14 different serotonin receptor subtypes have been found in mammals, and they are divided into 7 families (5-HT1 to 5-HT7 receptors) (Ozma et al., 2022; Berger et al., 2009). Except for the ligand-gated ion channel 5-HT3 receptor, most of them are G protein-coupled receptors. 5-HT1A receptors, for example, are usually associated with Gi/o proteins and function as autoreceptors on serotonergic neurons or as postsynaptic receptors in areas like the hippocampus and amygdala. This results in the inhibition of adenylyl cyclase and a change of ion channels (Ozma et al., 2022; Tian et al., 2020). On the other hand, Gq/11 proteins are linked to 5-HT2A receptors, which are highly abundant in the cortex. The stimulation of phospholipase C causes intracellular calcium mobilization. 5-HT1B/1D, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT6, and 5-HT7 receptors are other important subtypes. Each of these receptors has unique signaling cascades and physiological functions, including gastrointestinal motility, mood, appetite, nausea, vasoconstriction, circadian rhythms, and cognition (Ozma et al., 2022; Qi, 2025). Serotonin's complex effects on brain function and peripheral physiology are supported by the different distribution and signaling pathways of various receptor subtypes, which can be indirectly impacted by dietary variables that change serotonin availability or neuronal membrane environments (Ozma et al., 2022; Martin et al., 2017; Höglund et al., 2019).

Most Trp in animals is catabolized and converted to bioactive compounds via the kynurenic pathway, which may have an effect on the stress response. Dietary changes that modify Trp availability to the brain have been used to study the function of the 5-HT system in human behavior, emotion, and cognition (Keszthelyi et al., 2009). Trp is a precursor of 5-HT in serotonergic neurons. The hydroxylation of Trp to the intermediate 5-hydroxytryptophan, which is later decarboxylated to 5-HT, initiates the 5-HT metabolic pathway. Because 5-HTP is quickly decarboxylated through the enzyme aromatic amino acid decarboxylase, tissue levels of 5-HTP tend to be low (Russo et al., 2009). Thus, the hydroxylation of Trp, which is controlled by the enzyme known as tryptophan hydroxylase, is the rate-limiting step in the production of 5-HT. This enzyme is exclusive to cells that make 5-HT and has two different isoforms, TPH1 and TPH2 (Keszthelyi et al., 2009).

Russo et al. provided the intriguing hypothesis that Trp may serve as a signal to the brain, alerting the 5-HT system of peripheral homeostasis issues, which might then be used to maintain homeostasis. Brain Trp availability and raphe 5-HTergic activity will be affected by plasma Trp concentrations, which are influenced by stress, physical activity, immune system activation, and dietary composition (Höglund et al., 2019; Keszthelyi et al., 2009). Such Trp-related alterations in 5-HTergic activity may influence behavior and endocrine function through 5-HT projections to telencephalic and hypothalamic areas. One may argue that because teleost fish have 5-HT cell populations that are extra-raphe located and express the TPH1 isoform, they may be less sensitive to changes in Trp availability, making such impacts less significant.

Nonetheless, the raphe 5-HTergic cells in teleosts and other vertebrates regulate a majority of brain areas with a broad projection pattern (Keszthelyi et al., 2009). However, the precise contribution of distinct serotonergic cell populations to the regulation of behavior and endocrine mechanisms remains incompletely understood (Höglund et al., 2019; Keszthelyi et al., 2009).

Gut-derived regulation of the stress axis

Over the past 10 years, it has grown clear that the gut microbiota is essential for controlling the gut-brain axis. The gut is home to trillions of microorganisms, mostly bacteria but also yeasts, viruses, archaea, protozoa, and helminth parasites. Most of the evidence for the crucial role the microbiota plays in controlling stress-related changes in physiology, actions, and brain function comes from animal studies (Sekirov et al., 2010).

The hypothalamic-pituitary-adrenal [HPA] axis and the sympatho-adrenomedullary system are both main stress response pathways that are activated when stress is perceived by the brain's frontal cortex (Gurunathan et al., 2023; Tsigos and Chrousos, 2002). A key neuroendocrine system in the stress response, the HPA axis controls the production of glucocorticoids and affects immunity, digestion, mood, and behavior. Increased inflammation and dysregulation of the HPA axis have been identified as pathways for behavioral alterations brought on by stress (Gurunathan et al., 2023; Wang et al., 2017). Higher levels of

hypothalamic corticotropin-releasing factor, i.e., CRF, have been linked with more depressive and anxiety-like behaviors, and it has been demonstrated that male mice undergoing maternal separation [MS] and chronic unpredictable mild stress [CUMS] overproduce serum corticosterone in response to chronic stress (Gurunathan et al., 2023; Tian et al., 2020). The low-level negative feedback of corticosterone in the HPA axis was caused by downregulation of the glucocorticoid receptor, which was linked to elevated levels of inflammatory cytokines such as serum TNF- α and hippocampus IL-1. Similar overproduction of serum corticosterone was linked to increased anxiety and depressive-like behaviors in female mice under CUMS (Gurunathan et al., 2023; Amini-Khoei et al., 2019).

Amini-Khoei et al. shown that increased colonic inflammation, necrosis, and intestinal epithelium shedding were associated with dysregulated HPA axis function in MS; however, their investigation did not ascertain whether these changes were directly influenced by CRF receptor signaling (Gurunathan et al., 2023; Cryan and Lyte, 2014).

A significant finding was made in 2004 when it was shown that colonization with a specific kind of Bifidobacteria might correct the hyperactive HPA axis response to stress in GF mice (Foster et al., 2017). Further research findings have strengthened the association between gut bacteria and stress responsiveness. This study discovered that microbial populations may affect an organism's stress reactivity and that stress exposure during early life or adulthood can alter the microbiota makeup of the organism (Ortega et al., 2021). The amygdala, an essential brain region connected to stress, is likewise influenced by the microbiome. The amygdala controls physiological and behavioral reactions to stressful stimuli, especially those that cause worry or anxiety. Additionally, it is involved in social behavior and psychological development (Tsigos and Chrousos, 2002; Ortega et al., 2021) (Cowan et al., 2017; Sarkar et al., 2020).

Neuroactive metabolites affecting mood and cognition

Chemicals called neurotransmitters can travel via synapses between neurons to provide messages that control actions, including emotion, memory, and motility. Neurons may be excitable or inhibited by these chemical messengers (Strandwitz, 2018; Chen et al., 2021). The microbial regulation of neurotransmitter precursors influences neurotransmitter production, and some neurotransmitters are involved in the host-gut microbiota reciprocal interactions (Strandwitz, 2018). Recent research indicates that the gut bacteria generate short-chain fatty acids, bile acids, and neurotransmitters such as glutamate, GABA, serotonin, and dopamine (Strandwitz, 2018; Yano et al., 2015). Also, certain bacteria have genes for specific enzymes that can catalyze the conversion of substrates into precursors or neurotransmitters (Gurunathan et al., 2023; Dicks, 2022). Meanwhile, when certain bacterial metabolites function as signaling molecules, enteroendocrine cells may generate and release neurotransmitters (Gurunathan et al., 2023; Kovács, 2004). The brain must produce neurotransmitters from local pools of neurotransmitter precursors since neurotransmitters, including glutamate, GABA, dopamine, and serotonin, are unable to cross the blood-brain barrier (Chen et al., 2021; Tao et al., 2022).

A number of these precursors are nutritional amino acids (such as tyrosine and tryptophan) that enter the bloodstream, cross the blood-brain barrier, and are taken up by cells that produce the associated neurotransmitters. With the help of many host enzymes, the precursors are subsequently transformed through a few intermediary steps into functioning neurotransmitters, including serotonin, norepinephrine, and dopamine (Gurunathan et al., 2023; Tao et al., 2022). The generation of serotonin by enterochromaffin cells, which in turn stimulate the enteric nerve fibers to propel gastrointestinal motility, can be regulated by gut bacteria. Microbial compounds and other irritants are detected by the sensory receptors of enterochromaffin cells, which stimulate these cells and produce serotonin (Gurunathan et al., 2023; Xu et al., 2021; Cuesta et al., 2021). A local effect of serotonin may be generated by subsets of enterochromaffin cells that express the presynaptic protein synapsin interacting with chemically sensitive dorsal root neurons or the afferent fibers of vagal nerves that sense. These results suggest that local serotonin signaling, which affects the central nervous system, is modulated by the gut microbiota (Gurunathan et al., 2023; Tao et al., 2022). Extracellular vesicles from *P. hominis*, which are more prevalent in the aged, may be able to enter the brain through the vagus nerve and impair mice's cognitive capacities. Furthermore, *P. hominis* and *E. coli* are more prevalent in the feces of elderly mice and people (Tao et al., 2022; Lee et al., 2020). As a result, giving mice *P. hominis* and *E. coli* or *P. hominis* with extracellular vesicles or lipopolysaccharides via gavage also causes colitis and cognitive decline. However, both the infiltration of extracellular vesicles into the hippocampus and dementia in such animals are markedly inhibited by abdominal vagus nerve amputation (Gurunathan et al., 2023; Lee et al., 2020).

Foster & McVey Neufeld's groundbreaking study, which highlights the gut-brain axis's role in governing anxiety and depression, has enabled a more thorough understanding of the microbiome's impact on higher cognitive functions like

attention, reasoning, memory, learning, decision-making, and solving problems (Mayer et al., 2014). Mayer et al. support the paradigm shift in neuroscience by highlighting the gut-brain axis's significant influence on cognitive function (Mayer et al., 2014; Liu et al., 2015). Recent neuroimaging studies by Liu et al. expand our understanding of the gut microbiota's relationship to cognitive function (Mayer et al., 2014; Liang et al., 2022), while Liang et al. uses multi-omics data to elucidate the gut microbiome's effect on cognitive performance and brain anatomy (Mayer et al., 2014; Bairamian et al., 2022). Bairamian et al.'s discovery that gut microbiota-mediated neuroinflammation regulates Alzheimer's disease pathology and cognitive issues is a significant breakthrough in our knowledge of neurodegenerative illnesses (Mayer et al., 2014; Wasser et al., 2020).

In order to bring light on clinical outcomes, Wasser et al. explore the relationships among gut microbiota and cognitive function in Huntington's disease (Mayer et al., 2014; Diotaiuti et al., 2025). Researchers in the fields of psychology and neuroscience have grown increasingly interested in the connection between impulsive behavior and gut microbiota. Numerous investigations have brought focus to the possible influence of the gut microbiota on impulsive behaviors, cognitive processes, and decision-making (Mayer et al., 2014; Conlon and Bird, 2014).

7. RESPONSE DETERMINANTS AND INTERINDIVIDUAL VARIABILITY

Numerous human studies showed that nutrition significantly affects the gut microbiota's structural and functional ability; yet, newer research indicates that each person's gut microbiota response to dietary treatments differs greatly.

Since it is known that individuals have microbial taxa that are either responsive or resilient to dietary changes, it is exceedingly challenging to forecast how an individual's gut microbiota will react to a specific dietary intervention and, ultimately, how the person will benefit from it (Ghosh and Pramanik, 2021).

Composition and functioning of the microbiome

It is evident that the microbial composition and likely function in the gut are influenced by human nutritional components and dietary habits. The bacteria, viruses, archaea, and eukaryotic microorganisms that live in and on our bodies constitute the human microbiome (Postler and Ghosh, 2017). These microorganisms have the ability to significantly affect human physiology in both healthy and sick conditions. By supporting metabolic processes, fighting against infections, and educating the immune system, they influence the majority of our physiological processes either directly or indirectly (Lozupone et al., 2012).

A crucial initial phase in understanding how the microbiome contributes to both health and disease is characterizing the microbiome in healthy individuals. More than 1000 kinds of bacteria from a small number of known bacterial phyla, with Bacteroidetes and Firmicutes being the most common phyla, are normally present in healthy adult humans. When compared to other body regions, the gut microbiota is exceptionally varied, and the components of the gut microbiota vary significantly between people who appear to be in good health. The host's digestion and nutrition depend on the gut microbiota, which can result in nutrients from substrates that the host would not otherwise be able to digest. For example, it was recently discovered that a single locus in a certain species of *Bacteroides* has the ability to microbiologically digest xyloglucans, which are commonly found in agricultural crops like lettuce and onions (Ozma et al., 2022; Larsbrink et al., 2014; Shreiner et al., 2015). 92% of people had at least one of these rare *Bacteroides* species that could break down xyloglucans, according to an analysis of a public metagenome database. This shows how uncommon this ability is in members of the phylum Bacteroidetes and how essential it is to the human host (Ozma et al., 2022). With implications for nutrition and food, these studies show how humans have established positive connections with gut flora. Indigestible dietary fibers are broken down by microbes to produce short-chain fatty acids [SCFA], which are vital for intestinal mucosa energy and for regulating immunological responses and gut carcinogenesis. Butyrate, a bioactive SCFA found in the gut, has an intricate position in colon cancer that seems to depend on context and concentration, according to two recent preclinical studies. Because tumor formation was reduced by antibiotic therapy or a low-carbohydrate diet, both of which lower butyrate levels, and increased by providing butyrate to antibiotic-treated mice, these studies indicated that butyrate promotes tumor formation in transgenic mice via combined tumor suppression gene (APC) mutations and mismatch correction gene (MSH2) deficiencies (Ozma et al., 2022) (Ozma et al., 2022; Belcheva et al., 2014).

Host genetic, metabolic, and physiological factors

By shaping how microbial signals are perceived and processed, host-specific variables further affect response variability. Sensitivity to downstream signaling cascades and microbial metabolites is affected by genetic diversity in receptors, transporters, and metabolic enzymes (Goodrich et al., 2014). Endocrine status, immunological tone, intestinal barrier integrity, and baseline

inflammatory state all influence how sensitive the host is to signals from the gut. Age, sex, body composition, and disease status are examples of physiological variables which alter gut-brain communication by changing host metabolic pathways and microbial ecology (Falony et al., 2016). These interrelated host factors contribute to the explanation of why different people may experience different neurological or psychiatric responses to comparable microbial or metabolic exposures.

Implications for inconsistent clinical findings

The uneven and often mild effects observed in human nutraceutical intervention experiments can be strongly attributed to the combined variability resulting from microbial and host factors. Meaningful responses among physiologically diverse subgroups may be obscured by the prevalence of research that uses population-averaged outcomes without incorporating host phenotype or baseline microbiome function into consideration (Falony et al., 2016; Choi et al., 2021; Zeevi et al., 2015). Therefore, when assessed across different groups of people, therapies with true mechanistic promise may seem unsuccessful, especially in studies aimed at complex neuropsychiatric outcomes.

Need for stratified intervention designs

A move toward stratification and mechanism-informed intervention approaches will be necessary to address interindividual variability. Clinical studies can improve participant classification and signal detection by including host biomarkers, functional metabolic readouts, and baseline microbiome profiling (Falony et al., 2016; Zeevi et al., 2015). Phenotype-driven methods that combine biological markers and clinical features offer a path toward more accurate and repeatable results. Future nutraceutical research should focus on focused techniques that are particular to defined biological situations rather than aiming for uniform effects across varied populations. This strategy is expected to be crucial for attaining clinically applicable regulation of the gut-brain axis.

8. CLINICAL EVIDENCE BEYOND PROBIOTICS

Beyond live probiotic therapies, research investigations examining gut-brain axis regulation has progressively extended to non-viable microbial products, microbial metabolites, and dietary components that impact host signaling pathways. Postbiotics, short-chain fatty acids, fermented products containing inactivated microorganisms, and metabolite-enriched preparations have been the major subjects of human intervention research in this field. Results have been assessed in the gastrointestinal, neurological, and psychiatric domains (Salminen et al., 2021; Zhou and Chen, 2025). The results of this study offer preliminary evidence for the viability and biological significance of non-viable strategies in modifying gut-brain connection, even if the total amount of evidence is still small when compared to probiotic trials. The growing use of mechanistically informed designs in coming trials is a noteworthy asset; these designs frequently include immunological, metabolic, and neuroendocrine endpoints in addition to clinical symptom assessments (Salminen et al., 2021; Mayer et al., 2015). Supporting the concept that bioactive microbial products might have functional benefits independent of viability, specific studies have shown changes in gastrointestinal function, mood indices, or stress-related symptoms without requiring prolonged microbial colonization (Salminen et al., 2021; Sanders et al., 2019). The variety of interventions, research participants, and outcome metrics is still a significant drawback, though. The exploratory, short-term, and small size of many studies reduces statistical power and complicates cross-study comparisons (Zhou and Chen, 2025; Mayer et al., 2015).

In this area, endpoint selection is a recurring problem. While biological markers associated with gut-brain signaling, such as cytokines, microbial metabolites, and neuroendocrine hormones, may show high interindividual variability, clinical outcomes, such as mood scores or cognitive assessments, are frequently affected by contextual and psychological factors (Zhuang et al., 2024). The interpretation of intervention effects and the identification of responder subgroups have been hampered by the absence of validated, standardized biomarkers that accurately reflect gut-brain axis activity in humans. Because of this, many studies still have trouble directly attributing reported clinical changes to underlying molecular triggers.

As non-viable, metabolite-driven therapies advance toward broader clinical use, safety and regulatory issues become even more crucial. These methods may provide a better safety profile than live probiotics, notably for patients with severe neurological disorders or those with impaired immune systems (Sanders et al., 2019). However, postbiotic and associated nutraceutical regulatory regimes are still not consistently established across jurisdictions, with differences in categorization, quality control standards, and claims support (Salminen et al., 2021; Mayer et al., 2015). The transition of gut-brain-targeted nutraceuticals beyond probiotics into clinical practice will need addressing these issues with more precise regulatory standards and thorough safety investigations.

9. TRANSLATIONAL IMPLICATIONS AND RESEARCH PRIORITIES

Research on the gut-brain axis supports a change in the definition of nutraceuticals from general dietary supplements to specific modulators of microbe-host signaling. Emerging translational methodologies highlight nutraceuticals' ability to affect host immunological responses, metabolic pathways, and neuroendocrine signals through specific molecular interactions, rather than just changing the genetic makeup of microorganisms (Zeevi et al., 2015). This reinterpretation offers a more convincing biological justification for the design and assessment of interventions and is more in line with our current understanding of the gut–brain axis as a signaling network (Torres-Fuentes et al., 2017; Moțățăianu et al., 2023). The creation of phenotype-driven and biomarker-guided strategies for nutraceutical intervention is a top research focus. It has been demonstrated that responsiveness to gut-brain-targeted treatments is greatly affected by interindividual diversity in metabolic capacity, immunological tone, and microbiota composition (Wang et al., 2021). To improve trial stratification and identify responder subgroups, biomarkers such as circulating cytokines, microbial metabolites, barrier integrity markers, or neuroendocrine indicators may be used (Kearns, 2024). A similar approach to more individualized and mechanistically informed therapeutic techniques is provided by phenotype-based frameworks that combine biological profiles with clinical symptoms. Other translational issues involve dose optimization and intervention duration. Numerous research studies now in existence rely on empirically chosen dosages and brief intervention durations, which could not be sufficient to record significant alterations in gut-brain communication or subsequent neurological consequences (Zeevi et al., 2015; Cryan and Dinan, 2012). To create schedules for dosage that are both efficient and physiologically feasible, more focus on pharmacokinetic and pharmacodynamic concepts, such as metabolite bioavailability, tissue distribution, and temporal dynamics, is required. In order to differentiate between short-term effects and long-term physiological changes, longitudinal designs will be especially crucial.

Lastly, there are still significant gaps in disease-specific research. Fewer research studies have looked at translational nutraceutical techniques in neurodegenerative conditions, epilepsy, or severe psychiatric disorders, where gut–brain interactions may differ significantly from those in mood disorders and stress-related conditions, which account for a large portion of the current data (Cryan et al., 2019; Bairamian et al., 2022). Carefully chosen endpoints, interdisciplinary cooperation, and condition-specific mechanistic studies will be necessary to close these gaps. Together, these objectives show that in order to move gut-brain-targeted nutraceuticals from exploratory research to therapeutic relevance, a more organized and biologically based translational framework is needed (Figure 2).

Table 1. Major gut-derived metabolites involved in gut–brain signaling and their host receptors

Gut-derived metabolite class	Major metabolites	Primary host receptors / targets	Principal signaling pathways	Brain-relevant functional outcomes	Reference
Short-chain fatty acids [SCFAs]	Acetate, propionate, butyrate	GPR41 [FFAR3], GPR43 [FFAR2], GPR109A; HDACs	GPCR signaling, epigenetic regulation, immune modulation	Microglial maturation, reduced neuroinflammation, stress-axis regulation	Salva et al., 2021; Balaguer et al., 2021; Dalile et al., 2019; Canfora et al., 2019; Parada Venegas et al., 2019; Singh et al., 2014
Indole and tryptophan-derived metabolites	Indole-3-propionic acid, indole-3-acetic acid	Aryl hydrocarbon receptor [AhR], PXR	Immune tolerance, barrier integrity, neuroinflammatory control	Neuroprotection, modulation of mood and cognition	Noh et al., 2015; Mayo et al., 2019
Microbial neurotransmitter-related metabolites	GABA, dopamine precursors, serotonin modulators	GABA receptors [indirect], 5-HT receptors [indirect]	Enteroendocrine signaling, vagal activation	Modulation of anxiety, gut motility, stress responsiveness	Strandwitz, 2018; Yano et al., 2015; Dicks, 2022; Kovács, 2004; Chen et al., 2021;

					Tao et al., 2022; Xu et al., 2021; Cuesta et al., 2021
Bile acid derivatives	Deoxycholic acid, lithocholic acid	FXR, TGR5 [GPBAR1]	Endocrine signaling, metabolic regulation	Stress regulation, energy homeostasis, neuroendocrine effects	Canfora et al., 2019; Parada Venegas et al., 2019
Phenolic microbial metabolites	Urolithin A, phenylacetic acids	Nrf2, AhR, mitochondrial targets	Antioxidant signaling, mitophagy	Neuroprotection, cognitive resilience	Espín et al., 2013; Raya-Morquecho et al., 2025; Zhang et al., 2025; Huang et al., 2025
Peptidoglycan-derived muropeptides	MurNAc-containing fragments	NOD1, NOD2	NF-κB signaling, immune calibration	Reduced neuroinflammation via immune–brain crosstalk	Zhou et al., 2023; Llewellyn and Foey, 2017; Warner et al., 2013
Lipoteichoic acids and cell wall components	LTA from Lactobacillus spp.	TLR2, TLR6	Innate immune modulation	Indirect effects on neuroinflammation and HPA axis	Balaguer et al., 2021; Noh et al., 2015; Teame et al., 2020
Extracellular vesicle-associated metabolites	Bacterial EV cargo [lipids, proteins]	Pattern-recognition receptors; vagal pathways	Neuroimmune signaling, BBB interaction	Cognitive impairment or modulation [context-dependent]	Lee et al., 2020

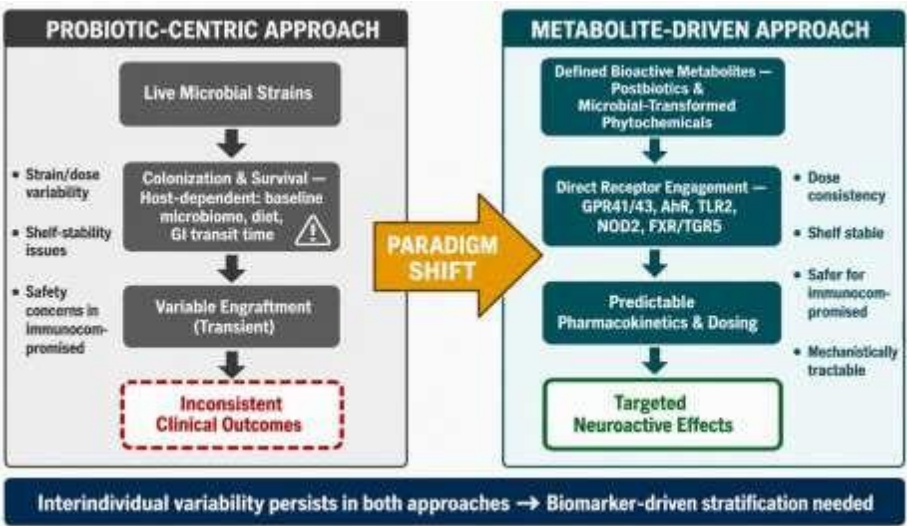


Figure 2. Comparison of the probiotic-centric and metabolite-driven nutraceutical paradigms. Live microbial strains depend on strain- and host-dependent colonization and survival, which can produce inconsistent clinical outcomes, whereas defined bioactive metabolites engage receptors directly with predictable pharmacokinetics and dosing. Interindividual variability persists in both approaches, underscoring the need for biomarker-driven stratification.

10. CONCLUSIONS

A conceptual change in gut-brain axis research is highlighted by this review, leading away from a probiotic-centric paradigm and toward a mechanistically defined framework centered around microbe-host signaling and microbial metabolites. Short-chain fatty acids, indole derivatives, phenolic metabolites, bile acid-related compounds, and other postbiotic components are displayed to be active signaling molecules that influence neuroinflammation, neurotransmitter dynamics, stress-axis regulation, and blood-brain barrier integrity in cellular, animal, and human studies. Rather than having secondary or accidental microbial impacts, these interactions show structured biochemical communication between the microbiota and host systems. The development of nutraceuticals is going to be significantly impacted by this interpretation. Conceptualizing nutraceuticals as modulators of defined metabolic and signaling pathways, rather than agents of microbial replacement, enables greater precision in formulation, dose selection, and safety assessment. While eliminating the ambiguities of microbial colonization and host compatibility, non-viable, metabolite-driven therapies provide useful benefits in stability, consistency, and regulatory alignment. This method prioritizes logical design over empirical supplements, bringing gut-brain nutraceutical research closer to systems biology and translational neuroscience. A variety of objectives will determine future development. To distinguish between short-term reactions and long-term physiological alterations, these include the creation of validated biomarkers that represent gut-brain signaling activity, the incorporation of host phenotype and microbiome function into trial design, and the optimization of dose and intervention duration. Since gut-brain pathways are unlikely to be similar across psychiatric, neurodevelopmental, and neurodegenerative conditions, disease-specific approaches will be crucial. When taken as a whole, moving past probiotics and toward metabolite-focused nutraceutical strategies offers a more rational and physiologically based route for converting gut-brain axis research into treatment options that are clinically significant.

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Author contributions

[Author One]: Literature search conceptualization, methodology, literature search, writing – original draft, writing – review and editing.

Conflict of interest

The authors declare no competing interests.

Data availability

No datasets were generated or analyzed during the preparation of this review.

Ethics statement

Not applicable. This article is a narrative review and does not contain any studies with human participants or animals performed by the authors.

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