

THE PHARMACOLOGY OF THE GUT–BRAIN AXIS: MICROBIAL METABOLITES AS EMERGING TARGETS FOR NEUROPSYCHIATRIC THERAPY

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ABSTRACT

The gut–brain axis (GBA) is a bidirectional communication network linking the gastrointestinal tract and the central nervous system through neural, endocrine, immune and metabolic pathways. Increasing evidence indicates that gut microorganisms are not merely passive inhabitants of the intestine but active biochemical partners capable of producing, transforming and regulating neuroactive molecules. Microbial metabolites—including short-chain fatty acids (SCFAs), tryptophan-derived indoles and kynurenine-related metabolites, secondary bile acids, γ -aminobutyric acid (GABA), dopamine-related metabolites and other small molecules—can influence neuroinflammation, blood–brain barrier integrity, microglial activity, neurotransmission, synaptic plasticity and hypothalamic–pituitary–adrenal-axis signaling. These mechanisms have been associated with depression, anxiety, autism spectrum disorder, schizophrenia, stress-related disorders and neurodegenerative disease. From a pharmacological perspective, the most important emerging concept is that microbial metabolites and their host receptors may represent druggable targets rather than only biomarkers of disease. Potential strategies include receptor-directed agonism or antagonism, metabolite replacement, enzyme modulation, psychobiotics, next-generation probiotics, precision prebiotics, postbiotics, fecal microbiota-based approaches and targeted delivery systems. At the same time, the microbiome can modify the pharmacokinetics and pharmacodynamics of conventional CNS medicines, creating an additional source of interindividual variability. This review summarizes the principal microbial metabolites involved in GBA signaling, their pharmacological targets and mechanisms, links to neuropsychiatric disorders, therapeutic opportunities, safety issues and translational challenges. A metabolite-centered pharmacological framework may contribute to future precision neuropsychiatry, although causality, standardization, long-term safety and clinically validated biomarkers remain major barriers.

KEYWORDS: gut–brain axis; microbiota; microbial metabolites; neuropharmacology; psychobiotics; short-chain fatty acids; tryptophan metabolism; bile acids; neuroinflammation; precision medicine.

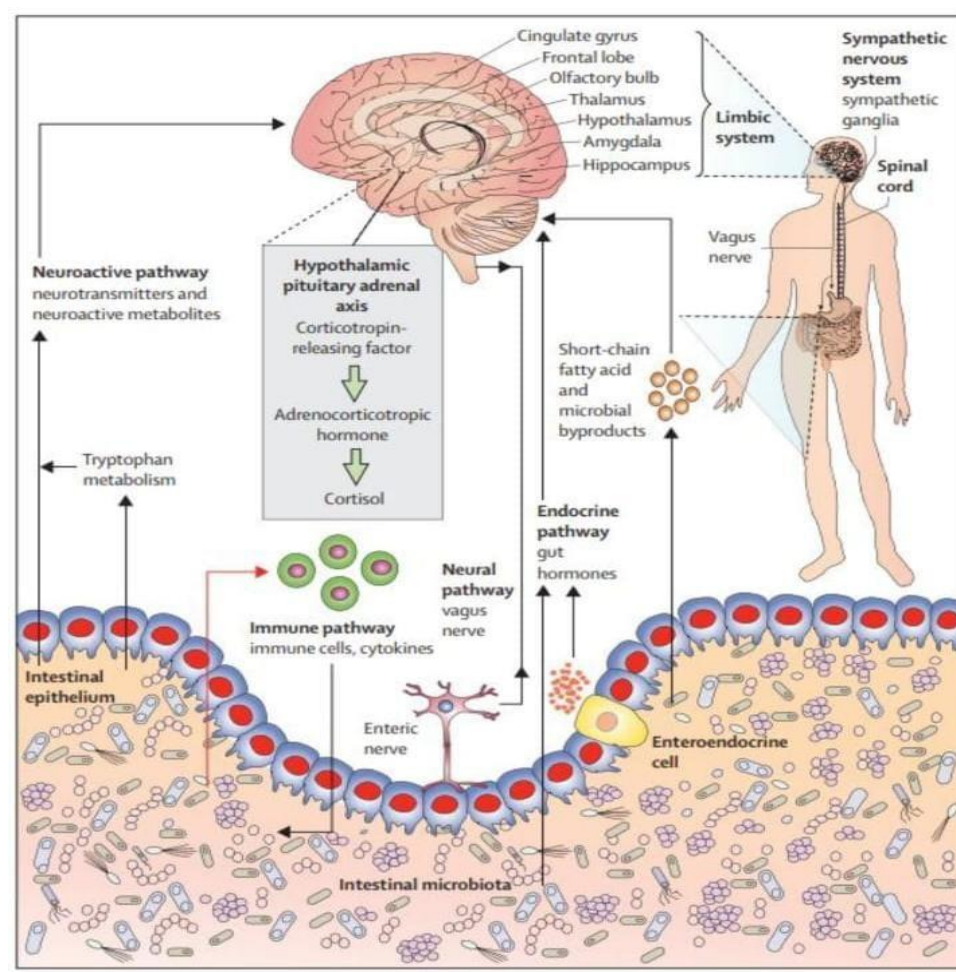
1. INTRODUCTION

Neuropsychiatric disorders represent a major therapeutic challenge because their pathophysiology involves interactions among genetics, immune signaling, metabolism, endocrine regulation, neuronal circuits and environmental exposures. Conventional pharmacotherapy has primarily focused on neurotransmitter systems such as serotonin, dopamine, noradrenaline, glutamate and GABA. Although these approaches have transformed psychiatric treatment, incomplete response, delayed onset, adverse effects and treatment resistance remain common. These limitations have encouraged investigation of biological systems that influence brain function beyond classical neuronal targets.

The gut–brain axis has emerged as one such system. It encompasses the intestinal microbiota, enteric nervous system, vagus nerve, immune system, hypothalamic–pituitary–adrenal axis, circulating metabolites and the

blood–brain barrier. Communication is bidirectional: the brain can alter intestinal motility, secretion and microbial ecology, while gut microorganisms can influence central nervous system function through metabolites, immune mediators and neural signaling.

Recent pharmacological literature has moved from describing associations between dysbiosis and brain disorders toward identifying molecular targets that could be manipulated therapeutically. Importantly, two complementary concepts are now developing. First, microbial metabolites may function as endogenous signaling molecules that can be pharmacologically enhanced, inhibited or mimicked. Second, the microbiome can modify the exposure and response to CNS-active drugs, creating a microbiome component of pharmacokinetics and pharmacodynamics. Recent 2026 reviews specifically emphasize these microbiome–drug interactions and the translational potential of pharmacological interventions along the GBA.^[1–3]



2. Objectives of the Review

- To summarize the major communication pathways of the gut–brain axis relevant to pharmacology.
- To classify important microbial metabolites according to their biochemical origin and pharmacological targets.

- To explain how microbial metabolites influence neuroinflammation, neurotransmission, neuroendocrine signaling and barrier function.
- To examine their relevance to major neuropsychiatric disorders.

- To identify emerging pharmacological strategies that target microbial metabolites, their receptors or their biosynthetic pathways.
- To discuss microbiome-mediated variability in CNS drug response and the barriers to clinical translation.

3. The Gut–Brain Axis as a Pharmacological System

3.1 Neural communication

The vagus nerve provides a major rapid communication route between the gastrointestinal tract and the brain. Microbial products can alter enteroendocrine signaling, intestinal sensory pathways and vagal activity. These signals can reach brainstem nuclei and influence autonomic regulation, stress responses and behavior. Importantly, the vagus nerve also represents a potential pharmacological interface because microbial effects may be modified indirectly through changes in intestinal metabolites and receptor activation.

3.2 Immune and inflammatory signaling

The intestinal immune system continuously senses microbial products. Dysbiosis, impaired epithelial integrity and excessive exposure to microbial components can promote systemic inflammatory signaling. Cytokines and innate immune pathways can influence microglial activation and neuronal function. Conversely, beneficial microbial metabolites may suppress inflammatory signaling and support immune

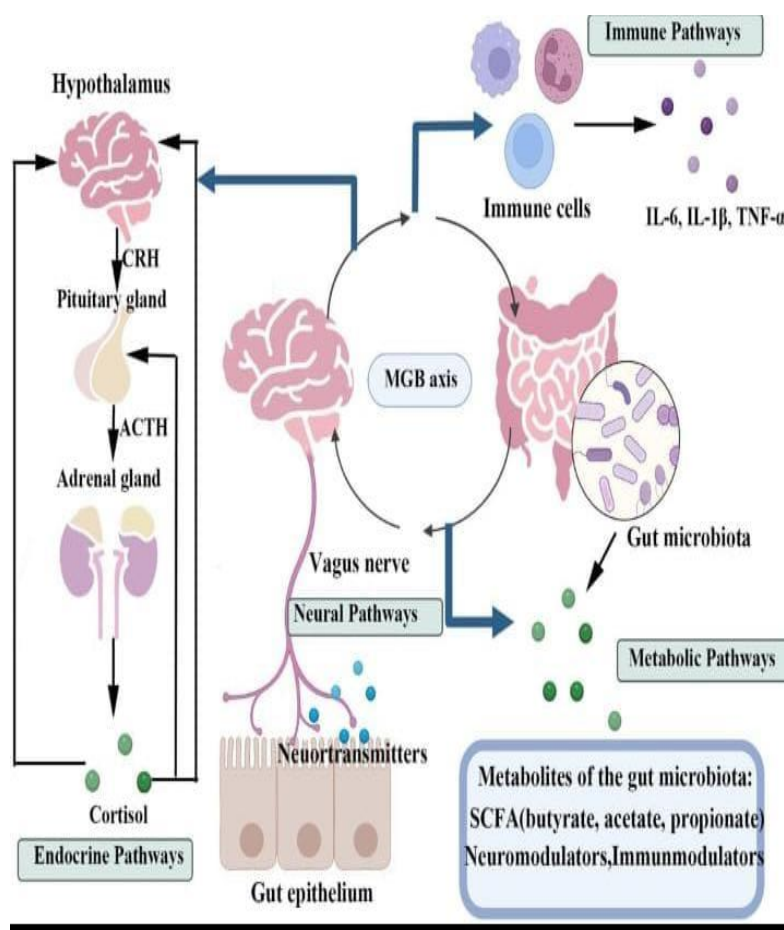
homeostasis. Toll-like receptor pathways, NF- κ B signaling and inflammasome-related mechanisms are therefore potential pharmacological targets.

3.3 Endocrine and HPA-axis signaling

Stress activates the hypothalamic–pituitary–adrenal axis and alters intestinal physiology. Microbial signals can influence glucocorticoid responses, while stress-related hormones can modify microbial composition and intestinal permeability. Persistent HPA-axis activation is relevant to depression, anxiety and stress-related disorders. Pharmacological strategies that normalize microbial metabolite signaling may therefore complement conventional approaches to stress biology.

3.4 Metabolic communication

The metabolic pathway is central to the modern concept of the GBA. Microorganisms transform dietary substrates into SCFAs, indole derivatives, bile acid metabolites and other small molecules. Some can enter systemic circulation and influence distant organs; others act locally on intestinal epithelial or immune cells and thereby alter downstream brain signaling. The 2026 IUPHAR review identifies SCFAs, tryptophan derivatives, bile acids and trimethylamine N-oxide among major metabolite classes with potential effects on neural, immune and behavioral processes.^[2]



4. Major Microbial Metabolites and Pharmacological Targets

Metabolite/class	Principal sources/pathways	Major targets/mechanisms	Potential neuropharmacological relevance
Short-chain fatty acids	Fermentation of dietary fiber by gut bacteria	FFAR2/FFAR3, HDAC inhibition, immune modulation	Neuroinflammation, microglial regulation, barrier integrity, mood
Tryptophan-derived indoles	Microbial tryptophan metabolism	AhR, barrier and immune signaling	Neuroinflammation, stress responses, serotonin-related pathways
Kynurenine-related metabolites	Host–microbial interaction in tryptophan metabolism	NMDA/aryl hydrocarbon receptor-related signaling	Depression, cognition, neurotoxicity/neuroprotection
Secondary bile acids	Microbial transformation of primary bile acids	FXR, TGR5 and immune/metabolic signaling	Neuroinflammation, metabolism, neuroprotection
GABA	Microbial glutamate decarboxylation	GABAergic signaling	Anxiety, stress, neuronal excitability
Dopamine-related metabolites	Microbial transformation of aromatic amino acids/catecholamines	Indirect monoaminergic and host metabolic effects	Behavior, reward and neurochemical homeostasis
TMA/TMAO	Microbial metabolism of choline/carnitine	Redox, vascular and inflammatory pathways	Potential links to cognitive and neurodegenerative disease

4.1 Short-chain fatty acids

Acetate, propionate and butyrate are the best-characterized SCFAs. They are produced mainly by bacterial fermentation of dietary carbohydrates. SCFAs can signal through free fatty acid receptors such as FFAR2 and FFAR3 and can also affect cellular function through epigenetic mechanisms, particularly histone deacetylase inhibition. These actions may influence immune-cell differentiation, intestinal barrier function, microglial signaling and neuroplasticity. Butyrate is especially interesting as a pharmacological tool because its epigenetic activity creates a mechanistic bridge between microbial metabolism and gene regulation in the nervous system.^[2,4]

4.2 Tryptophan-derived metabolites

Tryptophan is a key metabolic junction linking serotonin synthesis, host kynurenine metabolism and microbial pathways. Microorganisms can generate indole derivatives that interact with the aryl hydrocarbon receptor (AhR), influence epithelial integrity and modulate immune responses. Alterations in tryptophan availability and kynurenine pathway activity have been associated with depression and other neuropsychiatric phenotypes. Pharmacologically, this pathway offers several opportunities, including modulation of microbial tryptophan metabolism, inhibition of pathological kynurenine production and selective manipulation of receptor signaling.

4.3 Bile acid metabolites

Gut microbes convert primary bile acids into secondary bile acids that participate in host signaling. Beyond their classical digestive role, bile acids act as signaling

molecules through receptors including the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5). These pathways can influence inflammation, metabolism and cellular stress responses. Their contribution to CNS physiology is increasingly investigated, creating opportunities for receptor-directed pharmacology and metabolite-based therapeutics.

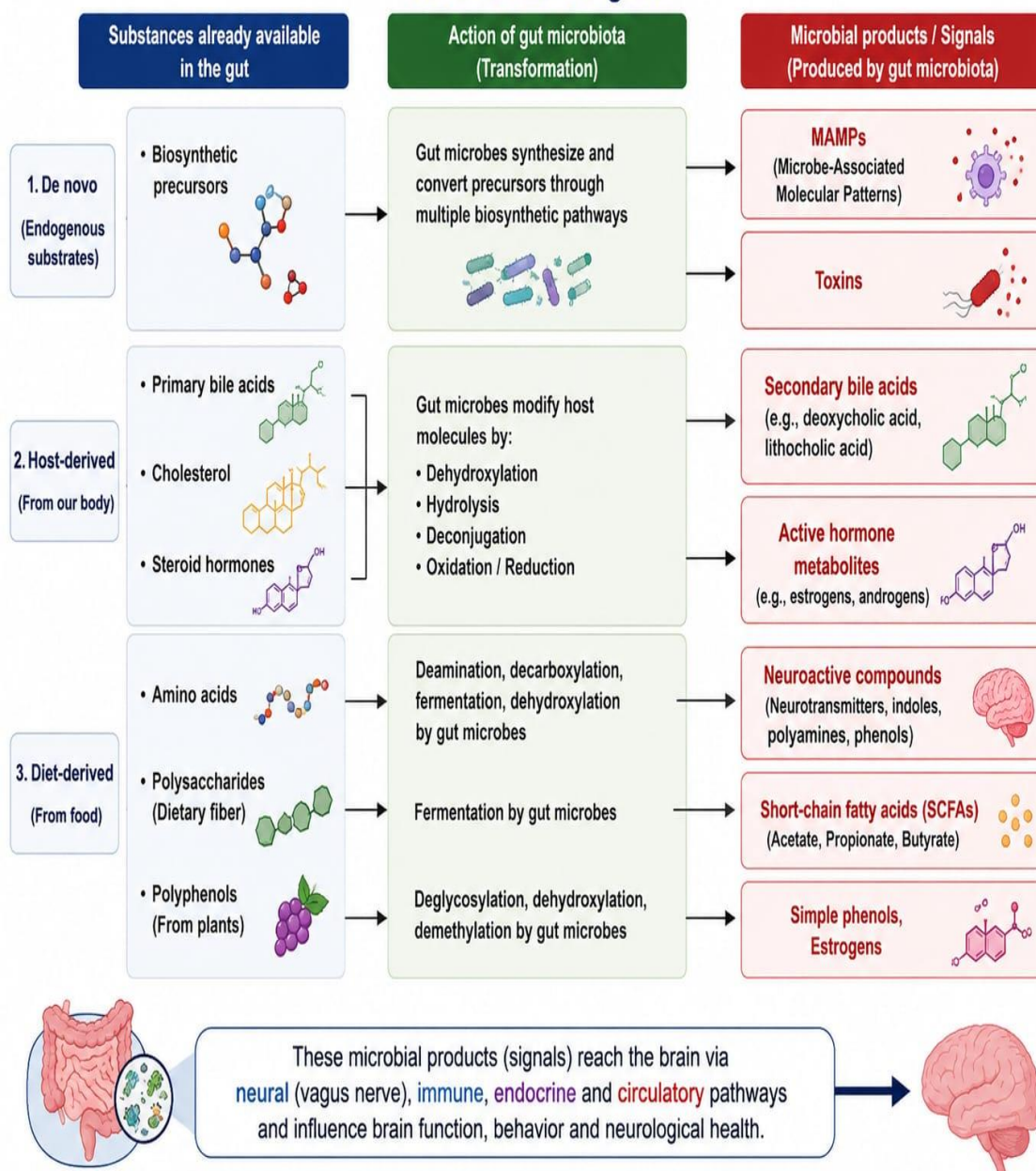
4.4 Microbial neurotransmitter-like metabolites

Several microorganisms can synthesize or modify neuroactive molecules, including GABA, serotonin-related compounds, dopamine-related metabolites and acetylcholine-associated pathways. Their ability to directly cross the blood–brain barrier varies substantially; therefore, their biological effects may occur through peripheral receptors, enteroendocrine signaling, immune modulation or vagal pathways rather than direct CNS penetration. This distinction is important when translating microbiome observations into pharmacological mechanisms.

4.5 Trimethylamine and trimethylamine N-oxide

Microbial metabolism of dietary choline, phosphatidylcholine and carnitine can generate trimethylamine, which is subsequently converted to trimethylamine N-oxide (TMAO) in the host. TMAO has been investigated in cardiovascular and metabolic disease and is increasingly studied in relation to neurological disorders. Because its effects may depend on dose, metabolic context and disease state, TMAO should be viewed as a candidate mechanistic biomarker and potential target rather than an established therapeutic target.

Gut Microbiota: Transformation of Substrates Present in the Gut into Bioactive Signals



5. Pharmacological Mechanisms Linking Microbial Metabolites to the Brain

5.1 Microglial modulation

Microglia are resident immune cells of the CNS and respond to systemic and microbial signals. Excessive microglial activation can contribute to neuroinflammation and neuronal dysfunction. Microbial metabolites such as SCFAs can influence microglial maturation and inflammatory signaling. This provides a pharmacological rationale for targeting metabolite-immune pathways rather than focusing exclusively on neuronal receptors.

5.2 Blood-brain barrier regulation

The intestinal barrier and blood-brain barrier form complementary interfaces between microbial products and host tissues. Dysbiosis and inflammatory signaling may compromise barrier integrity, while microbial metabolites can affect tight-junction proteins, endothelial signaling and immune tone. Restoration of barrier function may therefore represent an indirect route to modifying CNS disease.

5.3 Neurotransmitter regulation

Microbial metabolism can influence precursor availability and peripheral signaling associated with serotonin, GABA, dopamine and glutamate. However,

microbial production of a neurotransmitter does not automatically imply a direct increase in brain concentrations. Pharmacological interpretation should distinguish direct CNS effects from peripheral or immune-mediated effects.

5.4 Epigenetic mechanisms

SCFAs and related metabolites can influence histone acetylation and gene expression. This is particularly relevant because epigenetic regulation can produce persistent changes in neuronal and immune-cell phenotype. Microbial metabolites may therefore act as endogenous epigenetic modulators and could complement emerging epigenetic pharmacology.

6. Gut–Brain Axis in Major Neuropsychiatric Disorders

6.1 Depression

Depression is one of the most intensively studied conditions in GBA research. Altered microbial composition, inflammatory signaling, tryptophan metabolism and SCFA production have been reported in different patient populations. Recent reviews emphasize that microbial metabolites may influence serotonin/kynurenine balance, neuroinflammation, HPA-axis activity and neuroplasticity. However, heterogeneity among cohorts means that no single microbial signature can yet be considered a universal biomarker.^[2,5,6]

6.2 Anxiety and stress-related disorders

Stress can alter intestinal microbial ecology, permeability and metabolite production. Conversely, microbial signals may affect HPA-axis reactivity and anxiety-like behavior. GABA-related microbial pathways, SCFAs and tryptophan-derived compounds are among the mechanisms under investigation. Psychobiotic approaches are therefore being explored as adjunctive strategies rather than replacements for evidence-based psychiatric treatment.

6.3 Autism spectrum disorder

Autism spectrum disorder has been associated with altered gut microbial profiles and metabolite patterns in several studies. Proposed mechanisms include altered intestinal permeability, immune signaling, microbial metabolites and neurotransmitter-related pathways. Because autism is highly heterogeneous, future pharmacological strategies are more likely to involve molecularly defined subgroups than a single microbiome-based treatment.

6.4 Schizophrenia

Studies have reported associations between gut microbiota alterations, immune activation, tryptophan metabolism and schizophrenia. Potential pharmacological relevance includes interactions between microbial metabolism and dopamine-related pathways as well as effects on antipsychotic exposure and adverse effects. Strong causal clinical evidence remains limited.

6.5 Neurodegenerative disorders

The GBA is also being investigated in Parkinson's disease and Alzheimer's disease. Proposed mechanisms include intestinal barrier dysfunction, α -synuclein-related processes, microglial activation, systemic inflammation and microbial metabolite signaling. Pharmacological targeting of inflammatory and metabolic pathways may complement disease-specific CNS therapies, but human clinical evidence is still evolving.^[3]

7. Microbiome–Drug Interactions in CNS Pharmacology

The relationship between the microbiome and CNS drugs is bidirectional. Microbial enzymes can transform xenobiotics, alter absorption and influence systemic exposure. Conversely, antidepressants, antipsychotics and other CNS-active medicines can change microbial composition and intestinal physiology. A 2026 review highlighted potential microbiome-mediated effects on antidepressants such as selective serotonin reuptake inhibitors and tricyclic antidepressants, reinforcing the concept of pharmacomicrobiomics in neuropsychiatry.^[1]

This creates a clinically important possibility: two patients receiving the same dose may have different microbial communities capable of producing different metabolite profiles or modifying drug disposition. Future therapeutic drug monitoring may therefore incorporate microbiome-derived biomarkers alongside pharmacogenomic and conventional clinical variables.

8. Treatment strategies of gut brain disorders

Generally aim to restore gut microbota, reduce inflammation, improve gut function and regulate gut brain signaling or communication

1. Dietary intervention

High fiber diet ex. fruits, vegetables

2. prebiotics ex. garlic, banana, onion

3. probiotics ex. curd, yogurt, fermented food

4. stress management

The brain can influence intestine function through autonomic nervous system

Meditation

Yoga

Adequate sleep

5. pharmacological treatment

Treatment depends upon on the specific disorders

IBS. antispasmodics, laxatives

Depression/anxiety. physiotherapy anti depressants/anxiolytic treatment

Inflammatory bowel disease ex. corticosteroids, aminosaliclates

9. Emerging Pharmacological Strategies

9.1 Psychobiotics

Psychobiotics broadly refer to beneficial microorganisms or microbial-directed interventions intended to influence mental health through the GBA. Proposed mechanisms include SCFA production, modulation of inflammation, neurotransmitter precursor metabolism and restoration of

barrier function. Recent reviews have emphasized their potential in depression and mood disorders, but strain-specific effects and inconsistent clinical outcomes remain important limitations.^[7]

9.2 Postbiotics and defined microbial metabolites

Postbiotics offer an attractive pharmacological concept because they may provide defined microbial products without administering live organisms. Examples include purified metabolites, bacterial components and fermentation-derived products. A defined molecule could potentially provide more predictable dosing, quality control and pharmacokinetics than a complex live microbial preparation.

9.3 Receptor-directed metabolite pharmacology

Instead of changing the entire microbiome, future therapies may target host receptors activated by microbial metabolites. Candidate systems include FFAR2/FFAR3 for SCFAs, AhR for indole compounds, FXR/TGR5 for bile acids and selected immune receptors. This approach resembles conventional drug development and may facilitate dose optimization and pharmacodynamic biomarker development.

9.4 Microbial enzyme inhibitors

Selective inhibition of microbial enzymes could reduce production of harmful metabolites while preserving overall microbial diversity. This strategy may be particularly useful when a specific metabolite pathway is strongly linked to disease. However, microbial pathways are interconnected, and pathway inhibition may produce unintended metabolic consequences.

9.5 Next-generation probiotics and engineered bacteria

Engineered microbial strains may be designed to produce beneficial metabolites, consume harmful substrates or deliver therapeutic molecules locally in the intestine. Although this is scientifically attractive, containment, genetic stability, immunological safety and regulatory issues require careful evaluation.

9.6 Precision nutrition and prebiotics

Dietary substrates can selectively influence microbial metabolism. Precision nutrition aims to use individual microbiome and metabolic profiles to predict which substrates are most likely to produce beneficial metabolite patterns. Such interventions could become low-risk adjuncts to pharmacotherapy, although reproducibility and adherence remain challenges.

10. Pharmacological Targets: A Translational Framework

Target	Example strategy	Potential benefit	Major limitation
FFAR2/FFAR3	Selective agonists or SCFA mimetics	Immune/metabolic and barrier modulation	Systemic effects and tissue specificity
AhR	Selective agonists/modulators of indole signaling	Immune and barrier regulation	Context-dependent effects
FXR/TGR5	Receptor agonists/modulators	Bile-acid signaling and metabolic control	Complex CNS translation
Microbial enzymes	Selective enzyme inhibitors	Reduce disease-associated metabolites	Microbial redundancy
HDAC-related pathways	Butyrate or selective epigenetic modulators	Neuroplasticity and anti-inflammatory effects	Off-target epigenetic effects
Microbial taxa	Defined probiotics/next-generation strains	Restore functional metabolite production	Strain specificity and variability

11. Clinical Evidence and Current Limitations

Despite substantial mechanistic evidence, clinical translation remains incomplete. Recent 2025–2026 reviews emphasize heterogeneity in microbiome composition, diet, medication exposure, geography, age and sampling methods. Associations identified in cross-sectional studies do not establish causality. In addition, fecal microbial composition may not accurately represent metabolically active organisms or mucosal communities.^[1–3,5]

A second challenge is the difference between microbial abundance and microbial function. Two individuals may have different bacterial species but produce similar metabolites, while apparently similar microbial communities may differ in metabolic output. Consequently, metabolomics and functional pathway

analysis may be more informative than taxonomic profiling alone.

Clinical trials also need standardized endpoints. Symptom scales, inflammatory markers, metabolite concentrations, microbiome profiles, drug exposure and functional outcomes should ideally be integrated. Longitudinal sampling is particularly important because microbiome composition and metabolites change over time and in response to diet and medication.

12. Safety Considerations

Microbiome-directed pharmacology should not be assumed to be inherently safe. Live microbial interventions may pose risks in immunocompromised patients, and broad microbiome manipulation may produce unpredictable metabolic consequences.

Metabolites can also have dose-dependent or context-dependent effects. Therefore, pharmacological development should follow conventional principles of dose–response characterization, toxicology, interaction assessment and post-marketing surveillance.

13. Future Directions

- Metabolite-first precision psychiatry: classify patients according to functional metabolic signatures rather than microbiome composition alone.
- Integrated pharmacomicrobiomics: combine microbiome, metabolomics, pharmacogenomics and therapeutic drug monitoring to predict CNS drug response.
- Microbiome-derived biomarkers: validate circulating or fecal metabolites as predictors of treatment response and adverse effects.
- Selective receptor pharmacology: develop drugs that mimic beneficial microbial signaling without requiring broad microbiome manipulation.
- Engineered microbial therapeutics: create defined strains capable of producing or consuming selected metabolites under controlled conditions.
- Targeted delivery: use nanoparticles or colon-targeted formulations to deliver metabolite precursors, enzyme modulators or microbial therapeutics.
- Longitudinal clinical trials: determine whether metabolite changes precede clinical improvement and whether they are causal or secondary.
- Regulatory standardization: establish quality, potency, stability and safety standards for psychobiotics and postbiotic products.

14. Research Gaps and Opportunities for B.Pharm Research

The gut–brain axis provides several feasible areas for undergraduate and postgraduate pharmacology projects. Examples include systematic mapping of microbial metabolite targets, in-silico screening of metabolite analogues against FFAR2/FFAR3 or AhR, comparative analysis of psychobiotic strains and SCFA production, evaluation of drug–microbiome interactions using published datasets, and development of conceptual pharmacokinetic models linking microbial metabolism to CNS drug exposure. Such projects can be designed as literature reviews, computational studies, laboratory experiments or translational proposals.

15. CONCLUSION

The gut–brain axis is evolving from a descriptive biological concept into an emerging pharmacological system. Microbial metabolites can influence brain function through immune, endocrine, neural, metabolic and epigenetic mechanisms, while conventional CNS medicines can reciprocally modify the intestinal microbiome. SCFAs, tryptophan-derived compounds, bile acid metabolites and other microbial products therefore represent potential biomarkers, mediators and pharmacological targets.

The most promising future direction is not indiscriminate manipulation of the microbiome but precision targeting of specific metabolic pathways and host receptors. Defined postbiotics, receptor-selective drugs, microbial enzyme inhibitors, next-generation probiotics and microbiome-guided pharmacotherapy could complement conventional neuropsychiatric treatment. However, clinical adoption requires stronger causal evidence, standardized analytical methods, validated biomarkers, reproducible clinical trials and long-term safety data. The integration of pharmacology, microbiology, metabolomics, neuroscience and precision medicine may ultimately create a new discipline of metabolite-informed neuropharmacology.

16. Suggested Conceptual Figure

Figure 1. Pharmacology of the gut–brain axis. Dietary substrates → gut microbiota → microbial metabolites (SCFAs, indoles, kynurenine-related metabolites, bile acids, GABA and other metabolites) → intestinal barrier / immune cells / enteroendocrine cells → vagus nerve, HPA axis and systemic circulation → blood–brain barrier → microglia, astrocytes, neurons and synaptic pathways → neuropsychiatric outcomes. A second bidirectional arrow should depict CNS drugs altering microbial composition and microbial enzymes altering drug metabolism and response.

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