Small-Molecule Modulators of the Gut–Brain Axis: Molecular Mechanisms, Therapeutic Potential, and Translational Challenges

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Abstract

The gut–brain axis is a bidirectional communication network connecting the gastrointestinal tract and central nervous system through neural, endocrine, immune, metabolic, and microbial pathways. Increasing evidence indicates that small molecules generated by the host, gut microbiota, or chemical modification of microbiota-associated pathways can influence intestinal barrier integrity, systemic inflammation, neurotransmission, microglial activation, neuroendocrine signaling, and brain function. [1,3] This has created a new therapeutic concept in which the microbiome is not necessarily targeted by broad-spectrum antimicrobial approaches, but instead is pharmacologically manipulated through specific metabolites, receptors, enzymes, and signaling pathways. Important molecular classes include short-chain fatty acids (SCFAs), tryptophan-derived indoles, bile acids, trimethylamine/trimethylamine-N-oxide (TMA/TMAO), phenolic metabolites, polyamines, and microbial-derived urolithins. [2,6] In parallel, synthetic and repurposed small molecules such as metformin and selective receptor ligands provide opportunities to modify microbiota composition or metabolite signaling.[7,8] This review summarizes the molecular architecture of the gut–brain axis, discusses major classes of small-molecule modulators and their mechanisms, and evaluates evidence from neurological, neuropsychiatric, metabolic, and gastrointestinal disorders. Particular emphasis is placed on G-protein-coupled receptors, histone deacetylases, aryl hydrocarbon receptor, pregnane X receptor, farnesoid X receptor, Takeda G-protein-coupled receptor 5, and microbial metabolic pathways. Current evidence suggests that metabolite-based modulation may offer greater specificity than nonspecific microbiome manipulation. However, most candidate molecules remain at the preclinical stage, and challenges involving pharmacokinetics, tissue selectivity, microbiome variability, dose optimization, and safety remain substantial. Future development will require integration of metabolomics, microbiome sequencing, chemical biology, pharmacology, and precision medicine.

Keywords: gut–brain axis; microbiota; small molecules; microbial metabolites; short-chain fatty acids; bile acids; tryptophan metabolites; indole-3-propionic acid; TMAO; neuroinflammation; neurodegeneration.

1.Introduction

The gastrointestinal tract and brain were historically considered functionally distinct organs. Contemporary research has established that these systems communicate continuously through a complex network involving the vagus nerve, enteric nervous system, hypothalamic–pituitary–adrenal axis, immune mediators, endocrine hormones, intestinal barrier function, and microbial metabolites [1,2]. The gut microbiota represents a major biochemical component of this network. Microorganisms residing in the gastrointestinal tract metabolize dietary nutrients and host-derived substrates into thousands of small molecules capable of influencing both local intestinal physiology and distant organs, including the brain. [2,3]

The microbiota–gut–brain axis is therefore a dynamic system in which microbial composition, microbial metabolic activity, diet, medications, immune status, and host metabolism interact continuously. Alterations in the microbiota and its metabolic output have been associated with depression, anxiety, autism-spectrum conditions, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis, stroke, and other neurological disorders.[3,9,11] Importantly, association does not necessarily establish causality. However, studies

using germ-free animals, fecal microbiota transplantation, metabolite supplementation, and receptor-targeting approaches increasingly indicate that selected microbial molecules can directly modify host physiology.[3,10]

A major development in this field has therefore been the transition from a purely microbiome-centered concept toward a metabolite-centered pharmacological model. Instead of attempting to eliminate or replace entire microbial communities, researchers are investigating whether specific chemical signals can be increased, decreased, mimicked, or blocked. Small molecules are particularly attractive because they can often be chemically optimized, administered at defined doses, and evaluated using established pharmacological approaches.

Small-molecule modulators of the gut–brain axis can broadly be divided into four categories: (1) naturally occurring microbial metabolites used directly as therapeutic agents; (2) synthetic agonists or antagonists of host receptors sensing microbial metabolites; (3) inhibitors of microbial metabolic pathways; and (4) conventional drugs that secondarily modify microbiota composition or microbial metabolism.[4,7,8] Major pathways include SCFA signaling, tryptophan–indole metabolism, bile-acid signaling, TMA/TMAO metabolism, and mitochondrial signaling involving microbial-derived urolithins.

2. Molecular Architecture of the Gut–Brain Axis

The gut–brain axis is a multidirectional communication system rather than a single anatomical pathway. Communication occurs through neural, immune, endocrine, metabolic, and barrier-mediated mechanisms. [1,3]

2.1 Neural communication

The vagus nerve provides one of the most important rapid communication pathways between the gastrointestinal tract and brain. Enteroendocrine cells and intestinal neurons respond to nutrients, microbial products, and mechanical stimuli and transmit signals through vagal afferents.[1] Microbial metabolites can influence enteroendocrine signaling and consequently alter central appetite, stress responses, mood, and cognition.

The enteric nervous system is also affected by microbial metabolites. Several neurotransmitters and neurotransmitter-related compounds can be produced or modified by intestinal microorganisms. Although many bacterial neurotransmitters may not directly cross the blood–brain barrier, they can alter local neuronal, immune, and endocrine pathways that subsequently communicate with the central nervous system.[3]

2.2 Immune and inflammatory signaling

The intestinal immune system represents another major interface. Dysbiosis, increased intestinal permeability, and bacterial products such as lipopolysaccharide can promote systemic inflammation.[1,3] Circulating inflammatory mediators may subsequently affect the blood–brain barrier and activate microglia.

Conversely, microbial metabolites with anti-inflammatory properties can reduce peripheral and central inflammatory responses. SCFAs, indole derivatives, and selected bile acids have all been implicated in this process. [4,6]

2.3 Endocrine and metabolic signaling

The gut produces numerous hormones, including glucagon-like peptide-1, peptide YY, cholecystokinin, and ghrelin. Microbial metabolites can influence enteroendocrine cells and modify hormone secretion.[4] Bile acids, for example, activate TGR5 and can influence GLP-1 release. SCFAs can activate G-protein-coupled receptors expressed on enteroendocrine and immune cells.[4,5]

2.4 Microbial metabolites as chemical messengers

Microbial metabolites constitute one of the most chemically diverse components of the gut–brain axis. SCFAs, indole derivatives, secondary bile acids, TMAO, phenolic compounds, polyamines, and modified fatty acids can act locally or circulate systemically [2,6]. Some molecules can cross the blood–brain barrier, whereas others primarily affect the brain indirectly through immune, endocrine, or vagal mechanisms

3. Short-Chain Fatty Acids as Small-Molecule Modulators

SCFAs, particularly acetate, propionate, and butyrate, are among the best-characterized microbial metabolites. They are primarily produced through bacterial fermentation of dietary carbohydrates and fiber and regulate intestinal epithelial function, immune responses, metabolism, and nervous-system physiology. [4,5]

3.1 Receptor-mediated signaling

SCFAs activate free fatty acid receptors, particularly FFAR2/GPR43 and FFAR3/GPR41. These receptors are expressed in intestinal epithelial cells, enteroendocrine cells, immune populations, and other tissues.[5,12] SCFAs also influence cellular function through mechanisms independent of G-protein-coupled receptors.

Butyrate is additionally an inhibitor of histone deacetylases (HDACs). Through this epigenetic mechanism, butyrate can influence gene transcription, immune-cell differentiation, microglial function, and inflammatory signaling. [13]

3.2 Butyrate and neuroinflammation

Preclinical studies indicate that sodium butyrate can influence microglial morphology and inflammatory phenotype. Butyrate administration has been associated with changes in inflammatory cytokines and microglial activation. [13,14]

In experimental models of alcohol-related central nervous system injury, sodium butyrate improved behavioral abnormalities while reducing neuroinflammation, improving intestinal barrier integrity, and modifying microbiome-associated metabolic pathways. [14]

Butyrate may therefore act through several mechanisms:

- HDAC inhibition and epigenetic regulation;
- activation of SCFA-responsive receptors;
- improvement of intestinal tight-junction function;
- reduction of endotoxin translocation;
- modulation of microglial activation;
- regulation of peripheral immune responses.

3.3 Synthetic SCFA receptor modulators

Natural SCFAs have relatively modest receptor potency and limited selectivity. Consequently, synthetic high-affinity FFAR2/FFAR3 ligands have been investigated.[12] Such compounds could theoretically reproduce selected beneficial aspect of microbial SCFA signaling without requiring major changes in diet or microbiota.The major challenge is tissue selectivity because FFAR2 and FFAR3 occur in multiple tissues. Gut-restricted receptor agonists may therefore represent a particularly useful future strategy.

4. Tryptophan-Derived Microbial Metabolites

Tryptophan metabolism is one of the most promising molecular interfaces between gut microbiota and brain. Dietary tryptophan can undergo host metabolism through serotonin and kynurenine pathways or microbial conversion into indole derivatives.[6,15] Important microbial products include indole, indole-3-aldehyde, indole-3-acetic acid, and indole-3-propionic acid (IPA). These molecules can activate host receptors including the aryl hydrocarbon receptor (AHR) and pregnane X receptor (PXR). [6,15]

4.1 Aryl hydrocarbon receptor

AHR is a ligand-activated transcription factor that responds to structurally diverse endogenous and microbial molecules. Microbial tryptophan metabolites can activate AHR in intestinal epithelial and immune cells and thereby influence barrier integrity, cytokine production, immune-cell differentiation, and inflammation. [15] AHR represents an attractive but complex therapeutic target. Different ligands can induce different transcriptional programs, meaning that future drugs may need to act as selective AHR modulators rather than nonspecific agonists.

4.2 Indole-3-propionic acid

IPA is a microbial tryptophan metabolite with antioxidant and anti-inflammatory properties. Experimental studies suggest that IPA can improve intestinal barrier function and influence inflammatory pathways through AHR/PXR-associated mechanisms. [15,16] A randomized, double-blind, placebo-controlled study in healthy older adults receiving probiotics reported an increase in circulating IPA and changes in gut bacterial profiles and serum BDNF, supporting a potential relationship between IPA metabolism and neurobiological signaling. [17] Recent experimental studies have further reported that IPA supplementation can improve cognitive deficits, reduce neuroinflammation, preserve intestinal and blood–brain barrier integrity, and alter gut microbial composition in animal models. [18]These findings make IPA an important candidate for further translational investigation.

4.3 Tryptophan metabolism and psychiatric disorders

Tryptophan metabolism is also closely linked with depression and stress biology. Alterations in microbial metabolism may modify the availability of tryptophan for host serotonin and kynurenine pathways.[9]Changes in these pathways can potentially influence serotonin signaling, immune activity, neuroactive kynurenine metabolites, and neuroplasticity. However, clinical studies demonstrate substantial heterogeneity, emphasizing the need for personalized approaches.

5. Bile Acids as Gut–Brain Signaling Molecules

Bile acids are traditionally associated with lipid digestion, but they also function as signaling molecules. Primary bile acids synthesized in the liver are extensively modified by intestinal microorganisms, producing secondary bile acids with distinct receptor activities .[19] Two important receptors are farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5/GPBAR1).

5.1 FXR signaling

FXR regulates bile-acid synthesis, lipid metabolism, glucose metabolism, and intestinal endocrine signaling. Intestinal FXR activation can influence FGF19 production, establishing an endocrine pathway between the intestine, liver, and systemic tissues.[19,20]Altered bile-acid composition may therefore modify gut–brain communication indirectly through metabolic and inflammatory pathways.

5.2 TGR5 signaling

TGR5 is a membrane GPCR activated by selected bile acids. It is expressed in intestinal endocrine and immune cells and can stimulate GLP-1 secretion. Through GLP-1 and related pathways, TGR5 provides an indirect route through which intestinal bile-acid metabolism can influence brain physiology [20].

5.3 UDCA and TUDCA

Ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA) are hydrophilic bile acids that have attracted attention because of their anti-inflammatory, mitochondrial, antioxidant, and anti-apoptotic properties. [20,21] Experimental studies suggest that these compounds can influence mitochondrial function, oxidative stress, apoptosis, and neuroinflammation. Parkinson's disease has been a particularly important area of investigation. [21] Although early clinical studies have explored UDCA in Parkinson's disease, current evidence remains insufficient to establish UDCA as a disease-modifying neurological therapy. Further randomized clinical trials are required.

6. TMA/TMAO Pathway and Microbial Enzyme Inhibition

Trimethylamine is produced by gut bacteria from substrates such as choline and carnitine. The liver subsequently converts TMA into trimethylamine-N-oxide (TMAO). TMAO has been extensively studied in cardiovascular and metabolic disease and is increasingly being investigated in neurological disorders [22].

3,3-Dimethyl-1-butano

3,3-Dimethyl-1-butanol (DMB) provides an important proof of concept for targeting microbial metabolism. DMB, a structural analogue of choline, inhibits microbial TMA formation and can reduce circulating TMAO concentrations without directly eliminating the responsible bacteria .[22] This strategy is particularly attractive because it demonstrates that microbial metabolic pathways can be pharmacologically manipulated while potentially preserving broader microbial diversity.

TMAO and neuroinflammation

Experimental evidence suggests that TMAO may interact with inflammatory pathways, oxidative stress, mitochondrial function, and microglial activation [23]. However, the relationship between circulating TMAO and human neurological disease remains incompletely established.Therefore, TMA/TMAO inhibition should currently be considered an emerging research strategy rather than an established neurological treatment.

7. Urolithins and Other Microbial-Derived Molecules

Polyphenols provide another important example of microbiota-dependent pharmacology. Ellagitannins and ellagic acid present in foods can be metabolized by intestinal bacteria into urolithins, including urolithin A.Urolithin A has attracted considerable interest because of its ability to stimulate mitophagy and improve mitochondrial quality control [24]. Mitochondrial dysfunction is a central feature of aging and several neurodegenerative diseases, making this pathway particularly relevant.

Preclinical studies suggest that urolithin A may possess antioxidant, anti-inflammatory, anti-senescence, anti-apoptotic, and mitochondrial effects [24]. Human studies have demonstrated biological activity and tolerability, but neurological efficacy remains to be established.Other microbial metabolites, including phenolic acids and polyamines, may also influence neuronal function, although the evidence base is currently less mature than that for SCFAs, indole metabolites, and bile acids.

8. Conventional Small-Molecule Drugs as Gut–Brain-Axis Modulators

The gut–brain axis can also be modified by conventional drugs that were not originally developed as microbiome-targeting agents.

8.1 Metformin

Metformin is primarily an antidiabetic drug, but it can modify intestinal microbial communities and microbial metabolism. [7] Human studies indicate that metformin can selectively alter several bacterial populations, although the consistency and clinical significance of these changes remain uncertain. [7] Experimental studies have also linked metformin with gut–brain-axis signaling in antipsychotic-associated metabolic dysfunction.[8] These observations suggest that part of the pharmacological effect of conventional drugs may be mediated through interactions with intestinal microorganisms.

8.2 Other medications

Proton-pump inhibitors, statins, nonsteroidal anti-inflammatory drugs, and antidepressants can alter the composition or metabolic activity of the gut microbiota. [25] These changes may contribute to therapeutic or adverse effects.Consequently, future gut–brain pharmacology must consider drug–microbiome interactions as an important component of pharmacokinetics and pharmacodynamics.

9. Small Molecules and Neurodegenerative Diseases

9.1 Alzheimer's disease

Alzheimer's disease involves amyloid-β accumulation, tau pathology, synaptic dysfunction, oxidative stress, mitochondrial abnormalities, and chronic neuroinflammation. Several gut-derived metabolites have been proposed to influence these processes. [3,10] SCFAs may affect microglial activation and epigenetic pathways. Indole metabolites can influence AHR/PXR signaling and inflammatory responses. Bile acids may regulate mitochondrial and inflammatory processes, while urolithin A may enhance mitochondrial quality control. Recent experimental evidence suggests that IPA supplementation or increasing IPA-producing bacteria can improve cognitive outcomes in animal models of AD through mechanisms involving inflammation, barrier function, and host–microbial signaling. [26] However, controlled human trials are needed before these findings can be translated into clinical recommendations.

9.2 Parkinson's disease

Parkinson's disease is particularly relevant to gut–brain research because gastrointestinal abnormalities may precede classical motor manifestations. Altered gut microbiota, intestinal inflammation, α-synuclein biology, mitochondrial dysfunction, and neuroinflammation have all been implicated. [10,27] Potential small-molecule strategies include SCFA modulation, bile-acid signaling, tryptophan-derived metabolites, and compounds targeting inflammatory pathways.UDCA/TUDCA are particularly interesting because mitochondrial dysfunction and oxidative stress are important features of PD. However, clinical efficacy remains under investigation. [21,27]

9.3 Depression and anxiety

Depression is influenced by genetic, psychological, endocrine, metabolic, immune, and environmental factors. Nevertheless, microbial metabolites may affect serotonin biology, kynurenine metabolism, inflammation, HPA-axis activity, and neuronal plasticity. [9]SCFAs, indole metabolites, and microbiota-dependent regulation of tryptophan metabolism are therefore being investigated as possible components of antidepressant mechanisms.The substantial heterogeneity between patients suggests that future interventions may need to be metabolically personalized rather than based solely on psychiatric diagnosis.

10. Important Molecular Targets

Target/pathway	Representative molecules	Principal mechanism	Potential therapeutic relevance
FFAR2/GPR43	Acetate, propionate, synthetic agonists	GPCR signaling	Immune and metabolic regulation
FFAR3/GPR41	Propionate, SCFAs, synthetic ligands	GPCR signaling	Enteroendocrine and metabolic signaling
HDACs	Butyrate	Epigenetic inhibition	Neuroinflammation and plasticity
AHR	Indoles, IPA	Transcriptional regulation	Barrier and immune regulation
PXR	IPA and related indoles	Metabolic/barrier signaling	Intestinal protection
FXR	Bile acids, synthetic agonists	Nuclear receptor signaling	Metabolism and inflammation
TGR5	Secondary bile acids	GPCR signaling	GLP-1 and metabolic signaling
Microbial TMA lyases	DMB	TMA-production inhibition	TMAO reduction
Mitochondrial quality-control pathways	Urolithin A	Mitophagy	Neurodegeneration and aging

11. Therapeutic Strategies

11.1 Direct metabolite replacement

The simplest strategy is administration of a beneficial microbial metabolite. Examples include butyrate, IPA, UDCA, TUDCA, and urolithin A. Advantages include defined chemical composition and controllable dosing. However, oral administration does not guarantee that the compound will reach the target tissue at an appropriate concentration.

11.2 Receptor-selective pharmacology

Instead of administering natural metabolites, synthetic receptor agonists or antagonists can be developed. This approach may provide improved potency and pharmacokinetic properties.Tissue-selective compounds will probably be particularly important because receptors such as FFAR2, FFAR3, AHR, FXR, and TGR5 occur in several organs.

11.3 Microbial enzyme inhibition

Targeting microbial enzymes can modify metabolite production without eliminating the organism. DMB-mediated inhibition of microbial TMA production is an important proof of concept. [22] Similar approaches could potentially target enzymes involved in indole, bile-acid, phenolic, or neuroactive metabolite production.

11.4 Pharmacological reshaping of the microbiome

Conventional drugs such as metformin can change microbiota composition or metabolism.[7,8] This raises the possibility of developing "microbiome-active" small molecules that selectively favor beneficial metabolic pathways rather than targeting specific bacterial species.

12.Challenges and Limitations

12.1 Correlation versus causation

A metabolite associated with a neurological disorder is not necessarily a cause of that disorder. Disease, diet, medication, age, physical activity, and inflammation can independently influence microbial metabolism. [3]

12.2 Interindividual variability

The microbiome varies considerably among individuals. Consequently, the same dietary substrate may generate different metabolite profiles in different people.

12.3 Dose and pharmacokinetics

Physiological microbial concentrations may be substantially lower than concentrations used in experimental studies. Pharmacological doses may also activate receptors in ways that do not resemble normal microbial signaling.

12.4 Blood–brain barrier penetration

A central therapeutic effect does not necessarily require direct brain penetration. Nevertheless, compounds intended to act directly on neurons or microglia must reach the CNS at therapeutically meaningful concentrations.

12.5 Receptor pleiotropy

A single metabolite may activate several receptors. AHR is an important example in which different ligands can produce distinct biological outcomes. [15]

12.6 Safety and ecological effects Manipulating one microbial pathway may unintentionally cause accumulation of precursor molecules or redirect metabolism toward another potentially harmful pathway.

12.7 Lack of standardized biomarkers

Future clinical trials should measure target engagement through stool and plasma metabolomics, microbial functional genes, inflammatory biomarkers, receptor activation signatures, and neurological endpoints.

14. Conclusion

Small molecules represent a promising approach for translating gut–brain-axis biology into pharmacological therapy. Microbial metabolites such as SCFAs, indole derivatives, bile acids, TMA/TMAO-related compounds, and urolithins provide endogenous chemical signals capable of modifying intestinal barrier function, immune activity, endocrine signaling, mitochondrial homeostasis, microglial activation, and neuronal physiology. [2,6] Butyrate illustrates the therapeutic potential of SCFA-mediated receptor and epigenetic signaling; IPA demonstrates the importance of microbiota-derived tryptophan metabolites; UDCA

and TUDCA demonstrate the potential of bile-acid-based neuroprotection; and DMB provides proof of principle that selective inhibition of microbial metabolism can modify systemic metabolite exposure without necessarily eliminating the responsible microorganisms.[14,18,22] Nevertheless, the field remains predominantly translational and preclinical. Associations between microbiome composition and neurological disease are influenced by diet, medication, age, lifestyle, and disease itself. Therefore, development of clinically useful small-molecule gut–brain modulators requires rigorous demonstration of causality, target engagement, reproducible exposure, safety, and clinical efficacy.

The most promising future strategy is unlikely to involve one universal gut–brain drug. Instead, personalized combinations of metabolite replacement, receptor modulation, microbial enzyme inhibition, dietary intervention, and conventional pharmacotherapy may be required. Integration of microbiome sequencing, metabolomics, medicinal chemistry, pharmacology, and clinical neuroscience should enable the development of selective therapies capable of manipulating specific molecular conversations between the gut and brain.

13. Future Perspectives

The future of gut–brain pharmacology is likely to move toward precision metabolite therapeutics. Instead of classifying patients solely according to diagnoses such as depression or Parkinson's disease, patients could potentially be stratified according to their microbiome and metabolic phenotype.One patient might exhibit reduced butyrate production, another altered indole metabolism, and another increased TMA/TMAO production. Each metabolic phenotype could theoretically require a different pharmacological intervention.Multi-omics approaches will be essential. Metagenomics can identify microbial metabolic capacity, while metabolomics measures actual chemical output. Transcriptomics and proteomics can characterize host responses. Integrating these datasets may identify causal relationships between microbial genes, metabolites, host receptors, and neurological phenotypes. Another important direction is microbiome-sparing pharmacology. Traditional antibiotics broadly modify microbial ecosystems, whereas microbial enzyme inhibitors could selectively suppress harmful metabolic pathways while preserving microbial diversity.

Drug-delivery technologies may also improve the field. Colon-targeted formulations could deliver SCFAs, indoles, or receptor ligands directly to the intestine while reducing systemic exposure. Prodrugs and controlled-release systems may further improve stability and tissue targeting. Finally, clinical studies should combine neurological outcomes with gut and metabolic endpoints. A successful gut–brain therapy should ideally demonstrate target engagement together with clinically meaningful improvement in cognition, mood, motor function, or neuroinflammation.

References:

1. Aburto MR, Cryan JF. Gastrointestinal and brain barriers: unlocking gates of communication across the microbiota–gut–brain axis. *Nat Rev Gastroenterol Hepatol*. 2024;21:222–247.

2. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota–gut–brain axis. *Physiol Rev*. 2019;99(4):1877–2013.

3. Morais LH, Schreiber HL 4th, Mazmanian SK. The gut microbiota–brain axis in behaviour and brain disorders. *Nat Rev Microbiol*. 2021;19:241–255.

4. Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. *Nat Rev Immunol*. 2024;24:577–595.

5. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*. 2016;165(6):1332–1345.

6. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut*. 2021;70:1174–1182.

7. Petakh P, et al. Effects of metformin on the gut microbiota: a systematic review. *Mol Metab*. 2023;77:101805.

8. Cussotto S, Strain WD, Veronese N, et al. Metformin and the gut–brain axis in metabolic dysfunction associated with antipsychotic treatment. *Transl Psychiatry*. 2021.

9. Liu L, Wang H, Chen X, et al. Gut microbiota and depression: the current state of research and future directions. *Front Microbiol*. 2024.

10. Jiao F, Zhou L, Wu Z. The microbiota–gut–brain axis and small-molecule therapeutic strategies in Parkinson's disease. *Neurol Sci*. 2025;46:561–578.

11. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;13:701–712.

12. Milligan G. Ligands at the free fatty acid receptor 2/3 family of GPCRs. *Br J Pharmacol*. 2017.

13. Wang P, et al. Sodium butyrate and microglial function through HDAC-dependent signaling. *Neurobiol Dis*. 2018.

14. Wei H, Yu C, Zhang C, et al. Butyrate ameliorates chronic alcohol-related central nervous system injury by suppressing microglia-mediated neuroinflammation and modulating the microbiome–gut–brain axis. *Biomed Pharmacother*. 2023;160:114308.

15. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites and host signaling pathways. *Nat Rev Microbiol*. 2021.

16. Li J, Zhang L, Wu T, et al. Indole-3-propionic acid improves intestinal barrier function. *J Agric Food Chem*. 2021;69:1487–1495.

17. Gut microbiota-derived indole-3-propionic acid mediates neuroprotective effects associated with probiotic consumption in healthy elderly adults. *Clin Nutr*. 2023.

18. Indole-3-propionic acid attenuates neuroinflammation and cognitive deficits through modulation of inflammatory signaling. *J Agric Food Chem*. 2025.

19. Ridlon JM, Gaskins HR. Another renaissance for bile acid gastrointestinal microbiology. *Nat Rev Gastroenterol Hepatol*. 2024;21:348–364.

20. McMillin M, DeMorrow S. Effects of bile acids on neurological function and disease. *Biochim Biophys Acta Mol Basis Dis*. 2016.

21. Neuroprotective effects of ursodeoxycholic acid in Parkinson's disease and Alzheimer's disease. *Biomed Pharmacother*. 2026.

22. Wang Z, Roberts AB, Buffa JA, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell*. 2015;163:1585–1595.

23. TMAO-mediated inflammatory signaling and neuroinflammation in neurological disease. *PubMed-indexed experimental studies*. 2025.

24. Urolithin A in central nervous system disorders: therapeutic applications and challenges. *Front Pharmacol*. 2025.

25. Garg K, Mohajeri MH. Potential effects of the most prescribed drugs on the microbiota–gut–brain axis: a review. *Brain Res Bull*. 2024;207:110883.

26. Gut microbial-derived indole-3-propionate improves cognitive function in Alzheimer's disease. *PubMed-indexed experimental study*. 2025.

27. Microbiota–gut–brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets. *Signal Transduct Target Ther*. 2024;9:37.

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