The role of gut microbiota metabolites in the regeneration and protection of nervous tissue: a narrative review

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Abstract

The gut microbiota modulates various physiological functions in the human body, including digestion, immune regulation, gut barrier maintenance, and even nervous system activity. The bidirectional communication between gut microbes and the brain, known as the microbiota–gut–brain axis, is crucial for balanced metabolism. Recent studies have indicated that gut microbiota metabolites, such as short-chain fatty acids, indole derivatives, neurotransmitters, and other bioactive compounds, can positively impact neurogenesis, myelination, and axonal regeneration, suggesting their potential in therapeutic strategies for neuroprotection and neuroregeneration. Despite the growing number of studies on gut microbiota metabolites, understanding their role in neuroprotective mechanisms remains limited. This article reviews the classification, production, functions and therapeutic potential of the most well-known gut microbiota metabolites, as well as their impact on neurogenesis, synaptogenesis, energy metabolism, immune modulation, and blood–brain barrier integrity, which will provide a foundation for the study of gut microbiota metabolites in the field of biomedical engineering.

Key words: biomedical engineering; gut microbiota; metabolites; microbiota; neuroprotection; neuroregeneration; regenerative medicine; regenerative therapy

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Introduction

The human body contains, on average, more microbial cells than human cells do, with approximately 38 trillion bacteria compared with 30 trillion human cells.[1] Additionally, the total genome size of human commensal microbes far exceeds that of the host genome. These diverse microbial communities, collectively known as the microbiota, include not only bacteria but also archaea, eukaryotes, and viruses. Microorganisms inhabit various organs of the human body, such as the distal tracts of the genitourinary system, nasal cavities, and skin, but the majority reside in the gastrointestinal tract (GIT).[2] The gut microbiota shares a mutually beneficial relationship with its host, contributing to tissue homeostasis through numerous physiological functions. These functions include digestion, nutrient absorption, vitamin synthesis, maintenance of intestinal barrier integrity, protection against pathogens, cholesterol metabolism and modulation of both the immune system and the central nervous system (CNS).[3] The broad genetic and metabolic potential of the gut microbiota supports its involvement in nearly every aspect of human biology, from health maintenance and development to regeneration, aging, and disease.[4]

The roles of the gut microbiota extend far beyond the boundaries of the GIT. Intestinal microbes continuously interact with the gut and distant organs of the host through metabolites and signaling molecules produced by both the host and the gut microbes.[5] Growing evidence has revealed the bidirectional communication between the gut microbiome and the CNS, known as the "microbiota–gut–brain axis".[5-7] Communication between the gut microbiota and the brain occurs through various pathways, including the neuroendocrine system, vagus nerve, enteric nervous system (ENS), immune system, and circulatory system, via the production of neuroactive substances, metabolites, and hormones (**Figure 1**). Studies have demonstrated that the gut microbiota can produce or stimulate the production of neurotransmitters, including serotonin, dopamine, acetylcholine, and

γ-aminobutyric acid (GABA), as well as neuroactive metabolites such as short-chain fatty acids (SCFAs) and vitamins.[8-11] These substances influence both enteric neurons in the gut and neurons in the CNS. Overall, the interaction between the gut microbiota and the CNS is modulated directly by immune cells and nerve fibers and indirectly through the production of metabolites and hormones that can bypass the blood–brain barrier (BBB). Gut microbes and their metabolites interact with immune cells within gut-associated lymphoid tissues, thus regulating the production of proinflammatory and anti-inflammatory mediators.[12] The gut microbiota also indirectly impacts non-neuronal cells in the CNS, such as microglia, astrocytes, oligodendrocytes, and oligodendrocyte precursor cells.[13-15] These cells are essential for maintaining brain health and function through various roles, such as immune regulation, synaptic pruning, myelination, and neuronal support. When influenced by microbial metabolites or immune signals originating from the gut, these CNS cells can undergo changes in their activity levels, cytokine production, or responsiveness to signaling molecules.[4] Such interactions highlight the broader impact of microbiota metabolites in microbiota–gut–brain communications beyond neurons alone, contributing significantly to the overall balance and functionality of the CNS. Some gut microbiota metabolites have emerged as significant players in the modulation of BBB integrity, particularly within the context of neuroprotection and neuroregeneration.[16] By interacting with endothelial cells that constitute the BBB, microbial metabolites (e.g., SCFAs) can regulate the expression of tight junction (TJ) proteins, thereby enhancing barrier function.[17] This regulation is crucial, as a compromised BBB can lead to increased permeability and neuroinflammation, which are implicated in neurodegenerative diseases and neurological injuries. The potential of gut microbiota metabolites to enhance BBB integrity suggests therapeutic benefits for promoting neuroprotection. This involves limiting the entry of harmful substances into the brain and supporting neuroregeneration processes.

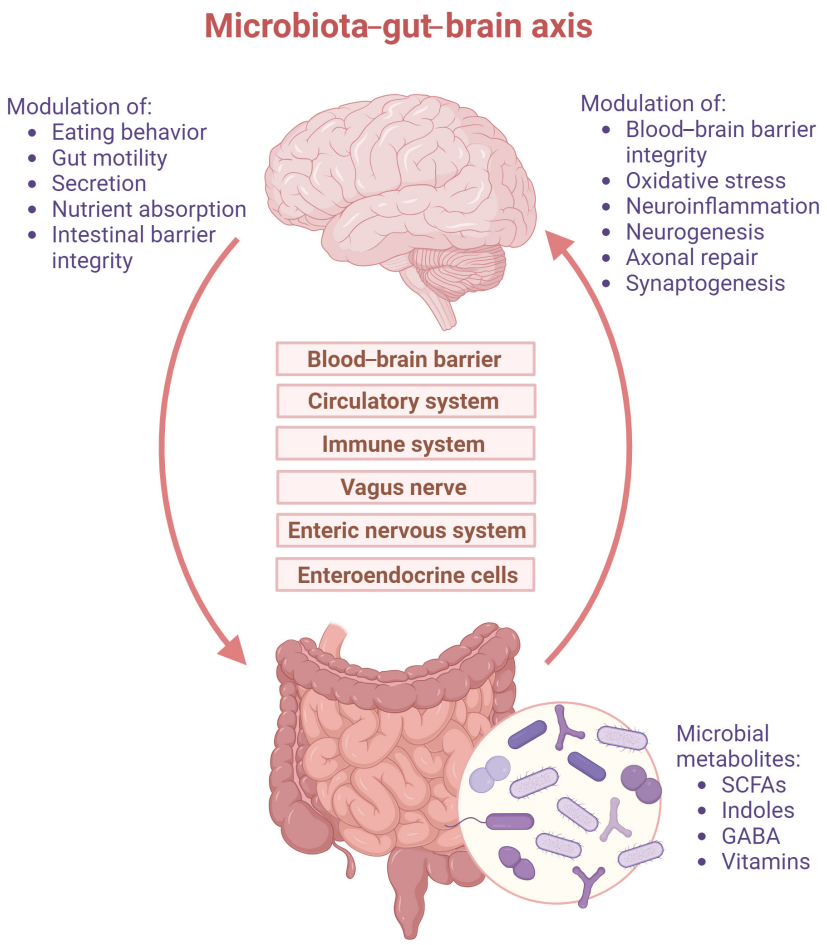

Figure 1: The microbiota–gut–brain axis
Note: Created with BioRender.com. GABA: γ-Aminobutyric acid; SCFAs: short-chain fatty acids.

Several studies have highlighted the significant role of gut microbiota metabolites as neuroprotective agents that promote nerve regeneration and repair.[18, 19] However, despite these findings, there has been no comprehensive summary of the functions of gut microbiota metabolites related to the protection and regeneration of nervous tissue. This gap has limited our understanding of the involvement of the gut microbiota in neuroregeneration. In this review, we aim to systematize the knowledge of gut microbiota metabolites within the microbiota–gut–brain axis. We begin with a brief introduction to how microbial metabolites impact nervous system function, followed by the classification of these metabolites. Next, we discuss their functions in detail, with a particular focus on their roles in regulating neurogenesis, synaptogenesis, and energy metabolism; modulating the local and systemic immune systems; and influencing the BBB. Finally, we discuss future research directions, therapeutic strategies and potential avenues for further exploration in this field.

Search Strategy

To conduct this literature review, various databases containing up-to-date information in the field were consulted: Web of Science, PubMed, ScienceDirect, Cochrane (Wiley), and Scopus were searched, and studies published between 2014 and 2024 were the focus. The search utilized specific keywords: "microbiota–gut–brain axis," "gut microbiota metabolites," "mycobiome," "neuroprotection," "regeneration," "neurotransmitter production," "blood–brain barrier integrity," "neurogenesis," "axonal repair," and "synaptogenesis." MeSH guidelines were followed to ensure the relevance of the literature reviewed. The search period was limited to articles published between 2014 and 2024, which guarantees the timeliness and relevance of the information included in this review. The following exclusion criteria were employed: (1) studies outside the period analyzed; (2) topics presented outside the scope of the review; and (3) books, conference proceedings, doctoral theses, and abstracts. Articles meeting scientific methodological standards and relevant to the review's subsections were included. Hence, this narrative review provides a summary of the involvement of gut microbiota metabolites in neuroprotection and neuroregeneration.

Role of Microbial Metabolites in the Microbiota-Gut-Brain Axis

The gut microbiota plays an essential role in the physiological development and maintenance of homeostasis in the peripheral and central nervous systems, which is why any significant disruption of the microbiota composition can lead to various serious disorders. For example, an imbalance in the gut microbiota, known as dysbiosis, has been associated with various neurological and psychological conditions, such as anxiety, depression, autism spectrum disorder and neurodegenerative diseases such as multiple sclerosis, Parkinson's disease and Alzheimer's disease.[4, 20] These findings underscore the significant role of the gut microbiota in crucial neurodevelopmental processes, including neurogenesis, myelination, microglial maturation, development and maintenance of BBB integrity.[7] One of the key mechanisms underlying microbiota–gut–brain crosstalk is the production of bioactive metabolites (**Figure 2**). The primary signaling pathway involving microbial metabolites occurs through the vagus nerve and spinal nerves of the autonomic nervous system. Microbial metabolites can signal directly to the vagus nerve via specialized enteroendocrine cells called "neuropod cells". Neuropod cells act as intermediaries, translating microbial signals into neural impulses that can be directly transmitted to the brain.[21] Notably, microbiota metabolites also directly influence enteric neurons and glial cells, which are integral components of the ENS, a part of the autonomic nervous system located in the GIT. The ENS plays a crucial role in coordinating gut functions, including motility, digestion, gut barrier function and intestinal mucosal immunity. Two ganglionated plexuses of the ENS, the submucosal plexus (Meissner's plexus) and the myenteric plexus (Auerbach's plexus), comprise an abundance of catecholaminergic, neuropeptide-expressing and GABAergic neurons.[22] The activity of these neurons can be modulated by the gut microbiota, which can produce neurotransmitters. Moreover, enteric neurons express Toll-like receptors, free fatty acid receptors and aryl hydrocarbon receptors (AhRs), which respond to other microbial metabolites, such as lipopolysaccharides (LPS), SCFAs and indole derivatives.[4, 22] Microbial metabolites, including norepinephrine, indole, indole-3-aldehyde, butyric acid, isobutyric acid and isovaleric acid, can also stimulate enterochromaffin cells, which release serotonin (also known as 5-hydroxytryptamine (5-HT)), a neurotransmitter involved in various physiological processes, including mood regulation and gastrointestinal function.[7]

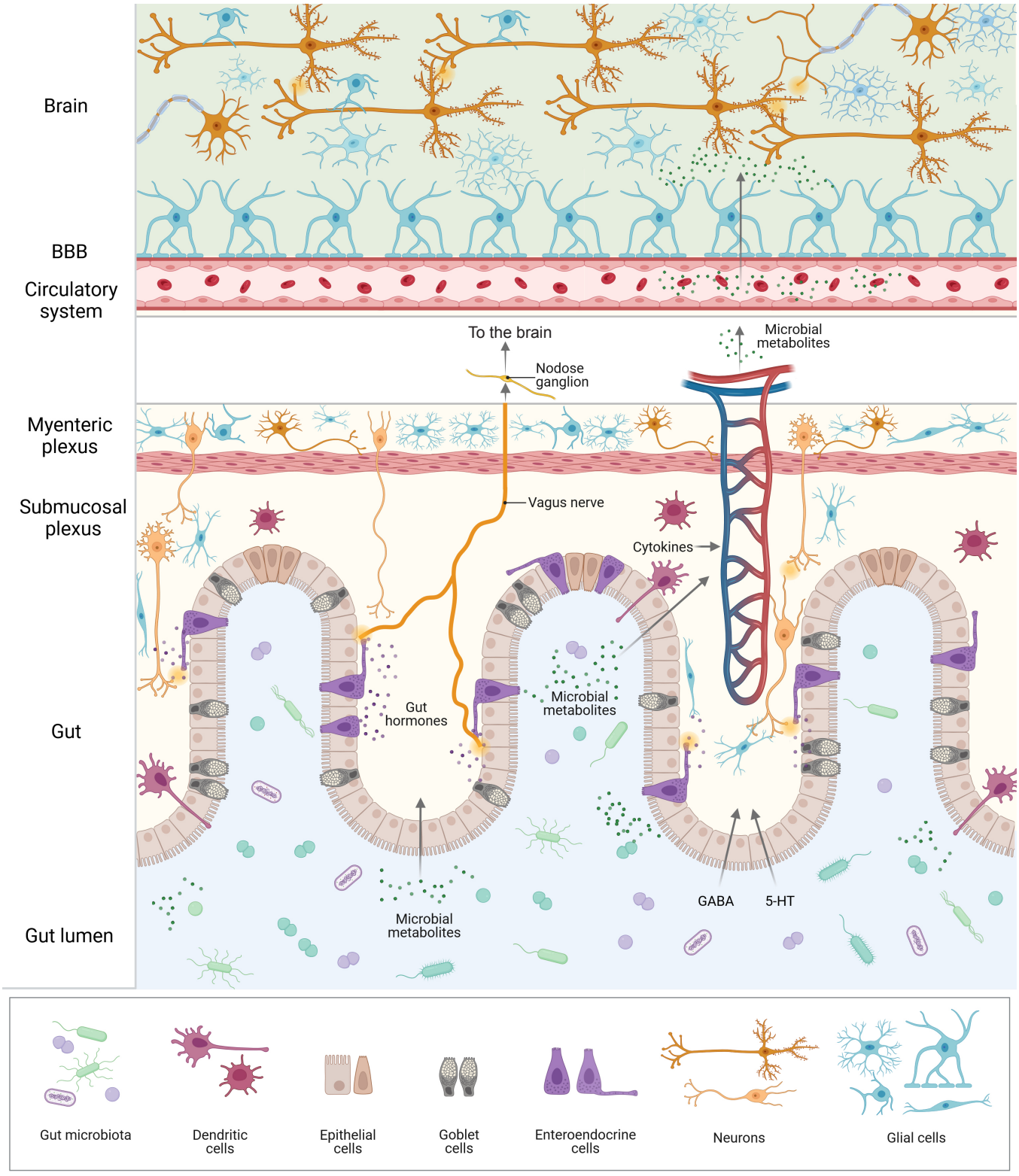

Figure 2: Mechanisms of action of gut microbiota metabolites on the nervous system

Note: Gut microbiota metabolites impact the nervous system through multiple pathways. Directly, microbial metabolites influence enteroendocrine cells in the gastrointestinal tract, which respond by releasing hormones and peptides that affect the enteric nervous system and communicate with the central nervous system (CNS). The vagus nerve transmits signals from microbial metabolites in the gut directly to the brain. Furthermore, dendritic cells in the gut interact with these metabolites, modulating cytokine production and initiating immune responses that can indirectly affect neuroinflammation and neuroimmune signaling. Microbial metabolites can also enter the bloodstream, allowing systemic circulation to transport them to the brain. Upon reaching the brain, they cross the blood–brain barrier (BBB) and affect CNS activity. Microbial metabolites can also affect the permeability of the BBB, a key factor in regulating what substances can enter the brain. This alteration in BBB permeability can indirectly impact brain function by modifying the microenvironment within the CNS. Created with BioRender.com. GABA: γ-Aminobutyric acid; 5-HT: serotonin.

Another possible underlying pathway of microbiota–gut–brain communication involves the circulatory system. Some microbial metabolites can cross the intestinal barrier and enter the bloodstream. From there, they can bypass the BBB and influence the CNS. This mechanism illustrates how the gut microbiota can indirectly affect brain function and behavior through the production of bioactive metabolites. For example, SCFAs such as butyric acid have been shown to cross the intestinal barrier and the BBB via monocarboxylate transporters located on endothelial cells, enabling SCFAs to interact with neuronal and glial receptors and influence gene expression in the brain.[23] In addition to bypassing the BBB and the intestinal barrier, microbial metabolites play an important role in maintaining barrier integrity, which is linked to the regulated passage of molecules and nutrients from the bloodstream to the brain. Several studies have highlighted the ability of microbial metabolites, such as SCFAs, branched-chain fatty acids (BCFAs) and indole derivatives, to increase the expression of TJ proteins such as claudins, occludin and zonula occludens-1 (ZO-1), thus regulating intestinal and BBB integrity.[16, 24-26] However, it is important to note that not all microbial metabolites can directly access the CNS though the bloodstream. Larger molecules, such as exopolysaccharides (EPSs), and neurotransmitters, including serotonin, GABA, acetylcholine, and noradrenaline, cannot cross the BBB, but they can impact enteric neurons and the vagus nerve, thus indirectly modulating CNS function.[27] In contrast, derivatives and precursors of neurotransmitters such as tyrosine or tryptophan can bypass the BBB, entering systemic circulation to be utilized for synthesizing neurotransmitters within the CNS.[27]

Microbiota-derived metabolites can also influence CNS functions by affecting immune responses and inflammation. They can trigger the release of pro- or anti-inflammatory cytokines, activate immune cells that circulate through the bloodstream, and impact BBB function, thus modifying the inflammatory status of brain cells.[12, 28] Metabolite-induced secretion of cytokines by immune cells can locally influence enteric neurons and modify vagus nerve signaling to the brain.[29] Research has shown that intestinal macrophages and their cytokine outputs can alter how enteric neurons respond to inflammatory signals and impact the apoptosis of these neurons. Moreover, cytokines affect the activity of enteric glial cells, which play crucial roles in supporting and regulating the function of enteric neurons by producing glial cell-derived neurotrophic factor. The production of this neurotrophic factor induced by SCFAs has been reported to stimulate the production of interleukin-22 (IL-22), thereby promoting the protection and restoration of the epithelial barrier.[29] Furthermore, microbial metabolites are recognized by Toll-like receptors expressed not only in enteric neurons but also in the smooth muscle cells of the intestinal wall and dendritic cells.[22] Within the CNS, the microbial metabolite-induced immune response can influence microglial phenotype and function, impacting their roles in synaptic pruning, neuroinflammation and neuroprotection.[4] For example, tryptophan metabolites such as indole derivatives can exert neuroprotective effects by modulating the kynurenine pathway, influencing the nuclear factor kappa B (NF-κB) signaling pathway and oxidative stress in the brain.[30]

Finally, microbial metabolites within the microbiota–gut–brain axis can influence energy metabolism. For example, SCFAs serve as key energy sources for intestinal cells. They can also cross the BBB and affect the energy metabolism of neurons and glial cells.[17] SCFAs can enhance mitochondrial function in brain cells, potentially boosting cognitive processes and protecting against neurological disorders. Moreover, SCFAs can act as signaling molecules that can modulate appetite-regulating hormones such as leptin and ghrelin.[23] By binding to specific receptors on enteroendocrine cells in the gut, SCFAs can stimulate the release of peptides that affect hunger and satiety signals sent to the brain. The gut microbiota has been reported to produce menaquinones and group B vitamins, which serve as critical cofactors in a wide array of metabolic reactions.[31-33]

As previously mentioned, the gut microbiota comprises a diverse range of microorganisms. However, the bioactive metabolites produced by archaea and fungi remain relatively understudied. Therefore, this review focuses mostly on bacterial metabolites. Furthermore, our scope is specifically aimed at discussing the role of gut microbiota metabolites in protecting and regenerating nervous tissue, which is why we do not discuss microbial metabolites that exhibit detrimental effects on nervous system function. The gut microbiota comprises six primary groups of bacteria: Bacillota (previously known as Firmicutes), Bacteroidota (previously known as Bacteroidetes), Actinomycetota (previously known as Actinobacteria), Pseudomonadota (previously known as Proteobacteria), Fusobacteriota (previously known as Fusobacteria), and Verrucomicrobiota (previously known as Verrucomicrobia), with Bacillota and Bacteroidota being the predominant phyla.[34, 35] Within these groups, bacteria from families such as *Lachnospiraceae*, *Oscillospiraceae* (previously known

as *Ruminococcaceae*), *Bacteroidaceae*, *Prevotellaceae*, and genera such as *Faecalibacterium, Bacteroides, Bifidobacterium, Lactobacillus, Prevotella, Roseburia*, and *Akkermansia* have been reported to produce health-promoting metabolites.[7, 36] The fungal community, known as the gut mycobiome, represents a smaller yet significant portion of the gut microbiota.[37] The most prevalent fungal phylum in the gut is Ascomycota, followed by Zygomycota and Basidiomycota. Within these groups, the genera *Candida*, *Saccharomyces*, *Malassezia*, *Cryptococcus*, *Aspergillus*, *Galactomyces*, *Trichosporon*, and *Cladosporium* are commonly found in the GIT.[38, 39] Gut fungi hold significant potential in the production of a wide array of metabolites that can be highly beneficial for both human health and gut bacteria. The gut mycobiota is known to produce various bioactive compounds, including β-1,3-glucan, a polysaccharide with powerful immunomodulatory properties. They also play crucial roles in the synthesis of vitamins, farnesol, tyrosol, and fatty acids that can support the growth and viability of beneficial gut bacteria.[37, 38] The archaea in the human gut microbiota are methane producers, with the predominant groups being Methanobacteriales, such as *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*, and Methanomassiliicoccales, such as members of the *Methanomethylophilaceae* family. Recent studies have shown that not all archaea in the human gut are methanogens, with viable haloarchaeal strains from the genus *Haloferax* being isolated from human feces.[40] It has been suggested that gut archaea, similar to gut bacteria, may produce beneficial metabolites such as SCFAs, tryptophan derivatives, GABA, and deconjugated bile acids.[41] However, research in this area is still limited and warrants further exploration.

Overall, microbial metabolites with health-promoting potential within the microbiota–gut–brain axis can be categorized into several major groups. Specifically, fatty acids (such as SCFAs, BCFAs, and conjugated polyunsaturated fatty acids), lactic acid, vitamins (including vitamins B and menaquinones), tryptophan derivatives (such as indole derivatives and 3-hydroxyanthranilic acid (3-HAA)), neurotransmitters (GABA, dopamine, and norepinephrine), deconjugated bile acids, polysaccharides (bacterial and fungal EPSs, such as dextran and β-glucans), fungal-derived secondary metabolites (tyrosol and farnesol) and polyphenol-derived secondary metabolites (equol and urolithins) were described. These metabolites influence nervous system function through a variety of mechanisms, ranging from affecting the maturation of microglia and neurogenesis to modulating synaptic plasticity and neurotransmitter synthesis. A summary of health-promoting microbial metabolites, including the taxa (families, genera or species) of microbes capable of producing these compounds, along with their effects on neurological function and the specific mechanisms involved, is provided in **Table 1.**

Neuroprotective Mechanisms Induced by Gut Microbiota Metabolites

Neuroprotection is considered one of the key therapeutic strategies for slowing neurological disease progression and promoting regeneration processes. The underlying mechanisms of neuroprotection involve mitigating oxidative stress, reducing neuroinflammation and mitochondrial dysfunction, improving BBB function, preventing glutamate excitotoxicity, correcting protein misfolding, maintaining proper autophagy, and inhibiting apoptosis.[42] Various microbial metabolites have been reported to influence these neuroprotective pathways in multiple beneficial ways.[43-47] For example, SCFAs, such as acetic, propionic, butyric and valeric acids, as well as BCFAs, such as isobutyric and isovaleric acids, have demonstrated significant anti-inflammatory and antioxidant properties.[7, 17, 48] Butyrate, in particular, can inhibit histone deacetylases, leading to the upregulation of genes involved in antioxidant defense, thus reducing oxidative stress. The influence of SCFAs on epigenetic regulation through histone acetylation and DNA methylation modulates the NF-κB signaling pathway and inflammatory cytokine production, reducing neuroinflammation.[49] An *in vitro* characterization of gut microbiota-derived bacterial strains revealed that *Parabacteroides distasonis* MRx0005 and *Megasphaera massiliensis* MRx0029 can produce butyric and valeric acids, which decrease neuroinflammation in glioblastoma cells and oxidative stress in neuron-like cells. Butyric acid specifically decreases IL-6 secretion in the presence of LPS.[18] Furthermore, microbiota-derived butyrate modulates mitochondrial activity in a lymphoblastoid cell line model of autism spectrum disorder, rescuing energy metabolism during oxidative stress.[50] Additionally, butyrate was found to promote the expression of TJ proteins, such as occludin and ZO-1, which are essential for the integrity of the BBB and intestinal barrier.[48, 51] In a mouse model of traumatic brain injury, the positive effect of butyrate on TJ proteins and BBB permeability resulted in the attenuation of neurological deficits, brain edema, and neuronal damage.[24]

Table 1: Microbial metabolites, the gut microbiota, and their health-promoting potential within the microbiota–gut–brain axis

Gut metabolites	Gut microbiota	Effects	Mechanism of action	Reference
Short-chain fatty acids (SCFAs): • Acetic acid • Propionic acid • Butyric acid • Valeric acid	*Acetobacteraceae* *Lachnospiraceae* *Oscillospiraceae* *Erysilotrichaceae* *Roseburia* *Bacteroides* *Bifidobacterium* *Blautia* *Eubacterium* *Clostridium butyricum* *Faecalibacterium prausnitzii* *Parabacteroides distasonis* *Akkermansia muciniphila* *Saccharomyces, Aspergillus*	↑Neurogenesis ↓Neuroinflammation ↓Neuronal apoptosis ↓Oxidative stress ↑Mitochondrial biogenesis ↑Dorsal root ganglia outgrowth ↑Integrity of BBB and intestinal barrier ↓Demyelination ↑Remyelination Anti-inflammatory effects Immunomodulation Modulation of enteroendocrine cells Modulation of synaptic plasticity and cognitive functions Modulation of neuronal energy metabolism	↑Proliferation of neural progenitor cells ↑BDNF expression ↑Neurotransmitter synthesis ↑GAP-43 ↓Activity of histone deacetylase ↓Proinflammatory cytokines Cholecystokinin-dependent stimulation of the vagus nerve ↓Activation of microglia and astrocytes ↑Maturation of microglia ↑Mature oligodendrocytes ↑Survival of Schwann cells ↑TJ proteins Energy source for cells Agonists of FFARs	13, 17, 18, 24, 37, 43, 48-50, 52, 53, 105, 106, 108, 113, 115
Branched-chain fatty acids (BCFAs): • Isobutyric acid • Isovaleric acid	*Lachnospiraceae* *Oscillospiraceae* *Peptostreptococcaceae* *Bacteroidaceae* *Blautia* *Ruminococcus* *Bacteroides*	↓Neuroinflammation ↓Neuronal apoptosis ↓Oxidative stress ↑Integrity of BBB and intestinal barrier Anti-inflammatory effects Modulation of enteroendocrine cells Modulation of neuronal energy metabolism	↓Activation of microglia and astrocytes ↓Pro-inflammatory cytokines ↓Activity of histone deacetylase ↑Neurotransmitter synthesis ↑TJ proteins Energy source for cells Agonists of FFARs	17, 51, 118, 128
Lactic acid	*Lactobacillaceae* *Bifidobacteriaceae* *Streptococcaceae* *Enterococcaceae*	↓Neuroinflammation ↑Neurogenesis ↑Axonal regeneration ↑Neuroplasticity and cognitive functions ↑Intestinal barrier integrity Immunomodulation Modulation of neuronal energy metabolism	↓Proinflammatory cytokines ↓Neutrophil infiltration ↑SIRT-mediated BDNF expression ↑GABA expression ↓Glutamate excitotoxicity Stimulation of the vagus nerve	55, 56, 109-111, 129-131
Conjugated polyunsaturated fatty acids: • Conjugated linoleic acid (CLA) • Conjugated linolenic acid (CLNA)	*Lactiplantibacillus plantarum* *Limosilactobacillus reuteri* *Lactococcus lactis* *Bifidobacterium breve*	↓Neuroinflammation ↓Oxidative stress ↓Lipid peroxidation Anti-inflammatory effects Anti-aggregative effect against $A\beta_{1-42}$	↑Proliferation of neural progenitor cells ↑Anti-inflammatory cytokines ↓Astrogliosis ↓ROS production ↑PPARα-induced peroxisomal β-oxidation	57-61
Group B vitamins: • Thiamin (B1) • Riboflavin (B2) • Niacin (B3) • Pantothenic acid (B5) • Pyridoxine (B6) • Biotin (B7) • Folic acid (B9) • Cobalamin (B12)	*Bacteroides fragilis* *Segatella copri* *Ruminococcus lactaris* *Corynebacterium glutamicum* *Propionibacterium freudenreichi* *Faecalibacterium prausnitzii* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* *Lactiplantibacillus plantarum* *Streptococcus thermophilus* *Lactococcus lactis*	↓Neuroinflammation ↑Neuronal survival ↓Demyelination ↓Neuronal death ↓Oxidative stress Cytoprotective and anti-inflammatory effects ↑Integrity of BBB and intestinal barrier Modulation of neuronal energy metabolism	↑Neurotransmitter synthesis ↓ROS production ↓Glutamate excitotoxicity ↓NF-κB-mediated transcription of inflammatory mediators ↑TJ proteins Cofactors of various enzymatic reactions in the metabolism of carbohydrates, fats, and amino acids Regulation of tryptophan metabolism via the kynurenine pathway	31, 33, 62-67, 112
Menaquinone (vitamin K2)	*Prevotella* *Propionibacterium freudenreichi* *Bacteroides fragilis* *Limosilactobacillus reuteri* *Lactococcus lactis* *Leuconostoc lactis* *Bacillus subtilis*	↓Neuroinflammation ↓Neuronal apoptosis ↓Oxidative stress Anti-inflammatory effects Mitochondrial protection ↑Integrity of BBB and intestinal barrier Anti-aggregative effect against $A\beta_{1-42}$ and α-synuclein	↓NF-κB-mediated transcription of inflammatory mediators ↓ROS production ↓iNOS expression ↑SOD and GSH-Px activity ↑Endothelial progenitor cell proliferation and migration ↑Sphingolipid synthesis	32, 44, 68, 69, 114
3-Hydroxyanthranilic acid (3-HAA)	*Pseudomonas* *Burkholderia* *Stenotrophomonas* *Xanthomonas* *Shewanella* *Bacillus*	↓Aging ↑Lifespan ↑Resistance to oxidative stress Immunomodulation	↑Nrf2/SKN-1 oxidative stress response pathway ↓PI3K/NF-κB signaling pathways	28, 30, 76, 77, 132
γ-Aminobutyric acid (GABA)	*Bacteroides fragilis* *Bifidobacterium angulatum* *Bifidobacterium adolescentis* *Lactiplantibacillus plantarum* *Levilactobacillus brevis* *Streptococcus thermophilus* *Lactococcus lactis* *Lactococcus garvieae* *Akkermansia muciniphila*	Modulation of gastrointestinal motility Modulation of synaptic transmission in the ENS Regulation of anxiety and depression Anti-nociceptive properties Immunomodulation	ENS excitatory neurotransmitter CNS inhibitory neurotransmitter ↓Neuron excitability ↓Glutamate excitotoxicity	9, 46, 119-122, 133, 134

Table 1 Continued

Gut metabolites	Gut microbiota	Effects	Mechanism of action	Reference
Indole derivatives: • Indole-3-aldehyde • Indole-3-acetaldehyde • Indole-3-acetic acid • Indole-3-lactic acid • Indole-3-propionic acid • Indoleacrylic acid • Kynurenic acid • 5-hydroxytryptophan (5-HTP) •Tryptamine	*Lactobacillus* *Bifidobacterium* *Bacteroides ovatus* *Bacteroides fragilis* *Clostridium sporogenes* *Clostridium caloritolerans* *Peptostreptococcus anaerobius* *Peptostreptococcus russellii*	↑Neurogenesis ↑Axonal regeneration ↑Neurite outgrowth ↑Functional integration of neurons in the hippocampus ↑Sensory neurological recovery ↑Spatial memory ↑Social behavior ↑Integrity of BBB and intestinal barrier ↓Neuroinflammation ↓Neuronal apoptosis ↓Oxidative stress Mitochondrial protection Modulation of enteroendocrine cells	↑BDNF expression ↑NGF expression ↑Neurotransmitter synthesis ↑Neutrophil chemotaxis toward the dorsal root ganglia ↑Synaptic plasticity ↑Inhibitory synaptic transmission in the hippocampus ↑ERK1 signaling ↑AhR signaling ↑TJ proteins ↑PGC-1α-mediated mitochondrial biogenesis ↓Synaptic overpruning ↓ROS production ↓Endothelial dysfunction ↓Activation of microglia ↓NF-κB-mediated transcription of inflammatory mediators ↑GPR30/AMPK/SIRT1 pathway Tryptophan metabolism via the kynurenine pathway	8, 19, 25, 26, 45, 70-75, 107, 116-118
Catecholamines: • Dopamine • Norepinephrine	*Lactiplantibacillus plantarum* *Bifidobacterium longum* *Bacillus subtilis* *Escherichia coli* *Serratia marcescens* *Streptococcus thermophilus* *Enterococcus faecium* *Eggerthella lenta* *Proteus vulgaris*	Modulation of synaptic plasticity and cognitive functions Regulation of intestinal motility, secretion and enteric neurotransmission	Neurotransmitters	119, 123, 135, 136
Deconjugated bile acids	*Lactobacillaceae* *Bifidobacteriaceae* *Streptococcaceae* *Oscillospiraceae* *Lactococcus lactis*	↓Oxidative stress Modulation of BBB and intestinal barrier Modulation of enteroendocrine cells Regulation of cholesterol absorption Immunomodulation	↓ROS production ↓Apoptosis of endothelial cells FXR-mediated inhibition of proinflammatory cytokine expression	79-83
Exopolysaccharides (EPSs)	*Lactobacillus* *Bifidobacterium* *Streptococcus* *Leuconostoc mesenteroides* *Weissella cibaria* *Candida*, *Saccharomyces*, *Aspergillus*	Antioxidant and immunomodulatory effects Anti-aggregative effect against $A\beta_{1-42}$ Mitochondrial protection ↓Neuronal apoptosis ↑Axonal regeneration	↓ROS production ↓iNOS expression ↑SOD and GSH-Px activity ↓NF-κB/MAPK signaling pathway Dectin-1-mediated cytokine production	38, 84-86, 88-90, 137
Equol	*Coriobacteriaceae* *Adlercreutzia equolifaciens* *Slackia equolifaciens* *Lactococcus garvieae* *Lactobacillus intestinalis* *Bifidobacterium breve*	↓Neuroinflammation ↓Neuronal apoptosis Cytoprotective and anti-inflammatory effects ↑Neurite outgrowth Modulation of synaptic plasticity and cognitive functions	↓NF-κB/MAPK-mediated transcription of inflammatory mediators ↓Microglia activation ↑Neurotrophins production through astrocytes Agonist of ERβ	47, 96, 97, 100
Urolithins	*Gordonibacter urolithinfaciens* *Gordonibacter pamelaeae* *Ellagibacter isourolithinifaciens* *Lactococcus garvieae* *Bifidobacterium longum* *Bifidobacterium adolescentis* *Bifidobacterium bifidum*	↓Neuroinflammation ↓Neuronal apoptosis Antioxidant and anti-inflammatory effects ↑Integrity of BBB and intestinal barrier ↑Neurite outgrowth	↓Proinflammatory cytokines ↑Anti-inflammatory cytokines ↓Activation of microglia, DCs and T cells ↓ROS production ↓iNOS expression ↓NF-κB/MAPK signaling pathway ↑TJ proteins	98, 99, 101-104, 138

Note: The directions of the effects and mechanisms are indicated by symbols as follows: increase/upregulation (↑) and decrease/downregulation (↓). 3-HAA: 3-Hydroxyanthranilic acid; 5-HTP: 5-hydroxytryptophan; AhR: aryl hydrocarbon receptor; AMPK: 5′-adenosine monophosphate-activated protein kinase; Aβ: β-amyloid; BBB: blood–brain barrier; BCFAs: branched-chain fatty acids; BDNF: brain-derived neurotrophic factor; CLA: conjugated linoleic acid; CLNA: conjugated linolenic acid; CNS: central nervous system; DCs: dendritic cells; ENS: enteric nervous system; EPSs: exopolysaccharides; ERK1: extracellular-signal-regulated kinase 1; ERβ: estrogen receptor β; FFARs: free fatty acid receptors; FXR: farnesoid X receptor; GABA: γ-aminobutyric acid; GAP-43: growth-associated protein 43; GPR30: G protein-coupled receptor 30; GSH-Px: glutathione peroxidase; iNOS: inducible nitric oxide synthase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa B; NGF: nerve growth factor alpha; Nrf2: nuclear factor-erythroid-derived 2-like 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K: phosphatidylinositol 3-kinase; PPARα: peroxisome proliferator-activated receptor alpha; ROS: reactive oxygen species; SIRT: sirtuin; SKN-1: skinhead 1; SOD: superoxide dismutase; TJ: tight junction.

Notably, SCFAs have also been shown to control the maturation and function of microglia, which are crucial cells involved in neuroinflammatory responses and the maintenance of brain homeostasis. An *in vivo* study with germ-free mice revealed that SCFAs can modulate the maturity and morphology of microglia, including the number of segments, branching points, terminal points and cell volumes.[52] Another study demonstrated that butyrate can reduce LPS-induced microglial activation and the depressive state.[53] Taken together, these findings indicate that SCFAs play crucial roles in microglial maturation and activation, possibly through epigenetic regulation that involves the inhibition of histone deacetylases. Interestingly, SCFAs, e.g., valeric acid, interfere with β-amyloid (Aβ) peptide 1–40 and 1–42 fibril formation *in vitro* and prevent α-synuclein monomers from pairing and aggregating into fibrils.[18] Given that microglia play crucial roles in clearing aggregated proteins and maintaining brain homeostasis, the ability of SCFAs to modulate protein aggregation may be somewhat explained by the influence of SCFAs on microglial function. Notably, SCFAs exhibit positive effects on health at low to moderate physiological concentrations. At these concentrations, SCFAs can reduce inflammation and promote the production of beneficial neurotrophic factors. However, at high concentrations, SCFAs can become detrimental, leading to increased inflammation and oxidative stress.[54]

Lactic acid, typically produced by lactic acid bacteria such as *Lactobacillus, Lactococcus,* and *Leuconostoc*, influences the production of GABA, a neurotransmitter that reduces neuronal excitability and protects against excitotoxicity, a process that leads to neuronal injury and death due to excessive stimulation by neurotransmitters. Additionally, lactate can be converted by various bacterial species into SCFAs, contributing to the overall metabolite pool. In the brain, owing to its ability to be metabolized into glutamate, lactate serves as an energy substrate for neurons, supports synaptic plasticity, and is essential for memory formation.[55, 56]

Several recent studies have provided comprehensive evidence that the gut microbiota can produce conjugated fatty acid metabolites from a fat-enriched diet. Conjugated fatty acids, such as conjugated linoleic acid (CLA) and conjugated linolenic acid, are known to exhibit anti-inflammatory and antioxidant activities.[57, 58] Furthermore, CLA and conjugated linolenic acid can impact the redistribution of ZO-1 and occludin, thus affecting the gut barrier and BBB functions. CLA was also shown to enter the brain and suppress neuroinflammation and the accumulation of Aβ. The neuroprotective effects of CLA are mediated through the upregulation of the anti-inflammatory cytokine IL-10 in astrocytes, a process induced by the activation of the nuclear transcription factor peroxisome proliferator-activated receptor gamma.[59] CLA may also help improve the breakdown of eicosanoids and oxidative stress products by increasing peroxisomal β-oxidation. This process enhances the body's ability to fight inflammation and oxidative stress, making CLA an effective anti-inflammatory and antioxidant agent. Moreover, CLA exerts a neuroprotective effect against glutamate excitotoxicity in the primary culture of rodent cortical neurons.[60] The antioxidant properties of CLA, including its ability to reduce reactive oxygen species (ROS) and increase the expression of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, help prevent age-associated neuronal damage in a mouse neurodegeneration model.[61]

Gut bacteria, such as *Bacteroides fragilis, Ruminococcus lactaris, Faecalibacterium prausnitzii, and Lactiplantibacillus plantarum*, have been reported to produce a variety of vitamins, including thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), biotin (vitamin B7), folate (vitamin B9), cobalamin (vitamin B12) and menaquinone (vitamin K2).[62-64] As enzymatic cofactors, group B vitamins play crucial roles in numerous physiological processes, including the metabolism of glucose, fatty acids, and amino acids; the tryptophan–kynurenine pathway; and the synthesis of various neurotransmitters and neurohormones, such as serotonin, dopamine, adrenaline, acetylcholine, GABA, glutamate, and melatonin.[33, 65] Since B vitamins are key players in metabolic pathways, it is not surprising that they modulate mitochondrial function, myelin formation, the response to oxidative stress and neuroinflammation.[66] For example, the administration of the thiamine-producing *L. plantarum* CRL 1905 strain was shown to inhibit neuronal death in a murine Parkinson's disease model by decreasing the expression of proinflammatory cytokines.[67] The gut microbiota also plays a major role in synthesizing vitamin K2.[32] This vitamin is essential for the synthesis of sphingolipids, which are components of myelin and cell membranes.[68] Vitamin K2 was shown to inhibit NF-κB signaling and the production of proinflammatory cytokines, such as IL-1β and IL-6.[69] The antioxidant properties of vitamin K2 further increase its neuroprotective potential. It neutralizes free radicals and reduces oxidative stress, which is common in the pathogenesis of many

neurodegenerative diseases.[44] In Parkinson's disease, treatment with vitamin K2 reduces the formation of α-synuclein fibrils and downregulates inducible nitric oxide synthase, thereby decreasing neuroinflammation and apoptosis. In Alzheimer's disease, vitamin K2 promotes sphingolipid formation while decreasing the formation of Aβ plaques, H_2O_2 cytotoxicity, ROS and apoptosis.[68] These actions collectively contribute to neuroprotection and the mitigation of disease progression.

Tryptophan metabolites, such as indole derivatives and 3-HAA, play a vital role in regulating neuroinflammation and oxidative stress through the kynurenine pathway.[19] Indole derivatives can modulate the activity of microglia and astrocytes, thus reducing the production of proinflammatory cytokines. Indole, indoxyl-3-sulfate, indole-3-propionic acid and indole-3-aldehyde can activate AhR signaling in astrocytes, thus suppressing neuroinflammation.[70] Microbiota-derived indoles have also been shown to inhibit microglial activation and the NF-κB signaling pathway in a mouse model of Alzheimer's disease, which in turn prevents Aβ accumulation and tau hyperphosphorylation. The same study has shown that indoles reverse injury to the gut barrier by increasing the expression of TJ proteins and improving the immunity of the host.[71] In addition to its anti-inflammatory activity, indole-3-propionic acid also has ROS-scavenging and BBB-protective properties.[25, 72] This metabolite was shown to reverse endothelial dysfunction by upregulating the expression of TJ proteins in endothelial cells.[73] Furthermore, indole-3-propionic acid protects hippocampal cornu ammonis area 1 neurons from ischemic damage and is suggested to modulate mitochondrial biogenesis in hippocampal interneurons through a mechanism mediated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha.[74] Additionally, microbiota-derived indole metabolites can reduce oxidative stress, inflammation, and neuronal apoptosis via the G protein-coupled receptor 30/5'-adenosine monophosphate-activated protein kinase/Sirtuin 1 pathway.[75] Another tryptophan metabolite, 3-HAA, also contributes to antioxidant defense by scavenging free radicals, thus protecting neurons from oxidative damage. 3-HAA reportedly enhances resistance to oxidative stress by activating the nuclear factor-erythroid-derived 2-like 2 (Nrf2)/Skinhead 1 signaling pathway, which promotes increased lifespan and reduced aging.[76] It was also demonstrated that 3-HAA can inhibit LPS-induced inflammation through the suppression of the phosphatidylinositol 3-kinase/NF-κB signaling pathways.[28, 77] Additionally, kynurenic acid, another tryptophan metabolite, exerts neuroprotective effects by modulating glutamate receptors, thus preventing excitotoxicity, which can damage neurons and impede neurogenesis.[30, 78]

Deconjugated bile acids produced by host–gut microbial cometabolism have been reported to modulate lipid metabolism and reduce oxidative stress, providing neuroprotective health benefits.[79-82] These bile acids also influence signaling pathways that regulate inflammation and cell survival, further contributing to brain health. Moreover, bile acids in the bloodstream affect BBB permeability by impacting TJ proteins such as occludin.[7] Deconjugated bile acids exhibit neurosteroid-like properties by interacting with receptors for neurotransmitters, including GABA and N-methyl-D-aspartate receptors. Their neuroprotective action may also be associated with the inhibition of Aβ accumulation, mitochondrial damage, and apoptosis.[79] Through their receptors in the brain and ENS, bile acids exert neuroendocrine effects via nuclear farnesoid X receptor, which is crucial for normal brain function, as evidenced by studies showing altered neurotransmitter levels, impaired cognitive function, and motor coordination upon farnesoid X receptor deletion.[79, 83]

EPSs produced by beneficial gut bacteria demonstrate neuroprotective properties by functioning as antioxidants and modulating immune responses. Several studies have highlighted the antioxidant activity of EPSs produced by lactic acid bacteria, which effectively scavenge superoxide anions and hydroxyl radicals.[84-87] EPSs also increase the activity of vital antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. For example, EPS from *Lacticaseibacillus rhamnosus* has been shown to mitigate oxidative stress and reduce inflammatory brain injury induced by D-galactose.[86] Moreover, EPSs reduce Aβ-mediated neurotoxicity in human neuroblastoma SH-SY5Y cells by decreasing apoptotic activity and stabilizing the mitochondrial membrane potential.[84, 85]

Like gut bacteria, gut fungi can also produce EPSs. These complex carbohydrate polymers play crucial roles in the gut environment, contributing to the formation of biofilms, modulating immune responses, and influencing the gut microbial community.[38] For example, the gut mycobiome can produce the polysaccharide β-1,3-glucan, which interacts with Dectin-1, a well-known pattern recognition receptor expressed by microglia and dendritic cells.[88] This interaction modulates cytokine expression, which can cross the intestinal barrier and

the BBB, thereby influencing brain function. Notably, β-1,3-glucan has been shown to promote CNS axon regeneration in a Dectin-1-dependent manner, likely through its effects on innate immunity.[88] Furthermore, β-glucan derived from *Saccharomyces cerevisiae* has been demonstrated to improve cognitive dysfunction via the gut–brain axis. Studies have shown that the administration of β-glucan leads to enhanced cognitive function and reduced pathological changes, including decreased Aβ plaque deposition, in Alzheimer's disease models.[89, 90] Additionally, β-glucan supplementation has been associated with beneficial alterations in the composition of the gut microbiota and the production of metabolites such as SCFAs. These changes contribute to the overall reduction in inflammatory factors and microglial activation in the cerebral cortex and hippocampus, ultimately controlling neuroinflammation and supporting brain health.[90]

Gut fungi are known to produce other types of bioactive metabolites, such as the phenolic alcohol tyrosol and the sesquiterpene alcohol farnesol.[38] Tyrosol and farnesol are both quorum-sensing molecules that play crucial roles in fungal communication and pathogenicity. In the gut environment, these compounds modulate fungal growth, biofilm formation, and the host immune response.[91] Although the effects of these compounds produced by gut fungi on the nervous system have not yet been documented, it is important to note that plant-derived tyrosol and farnesol are known as neuroprotective, antioxidant, and anti-inflammatory agents that can promote remyelination and synaptogenesis.[92-95] It is plausible that these compounds produced by gut fungi might exert comparable benefits on the nervous system. However, further research is needed to elucidate the specific roles of gut fungus-derived tyrosol and farnesol within the microbiota–gut–brain axis.

Some gut microbiota genera have demonstrated the ability to metabolize dietary polyphenols to produce microbiota-derived secondary metabolites, such as equol and urolithins.[96-99] This modification of polyphenolic compounds significantly increases their bioavailability, maximizing their absorption and potential health-promoting effects. For example, equol, a metabolite produced from soy isoflavones by certain gut bacteria, has shown estrogen-like neuroprotective effects.[47, 96, 100] It can reduce inflammation and oxidative damage in the brain, promote neuronal health and prevent the neurodegenerative changes associated with aging and disease. The antioxidant properties of equol are largely attributed to its interaction with estrogen receptor β, which activates the extracellular-signal-regulated kinase (ERK)/NF-κB signaling pathway, thereby influencing transcription, cytokine production, and cell survival.[97] The gut microbiota also metabolizes ellagic acid to produce bioactive secondary metabolites called urolithins.[98, 99, 101] Among these, urolithin A is notable for its potent anti-inflammatory and antioxidant properties. It induces mitochondria-selective autophagy, which helps to protect mitochondrial function during aging.[99] Urolithins have demonstrated promising neuroprotective effects by alleviating the damage induced by Aβ25-35, reducing lactate dehydrogenase leakage, decreasing ROS production, inhibiting neuroinflammation and neuronal apoptosis, and promoting neurite outgrowth.[102-104]

Role of Gut Microbiota Metabolites in the Regeneration of Nervous Tissue

The neuroprotective properties of gut microbiota metabolites suggest their potential role in promoting the regeneration of nervous tissue. These metabolites are believed to play crucial roles in essential processes vital for regeneration, such as neurogenesis, axonal repair, and synaptogenesis.[19, 20, 43] Furthermore, recent research underscores the pivotal role of these metabolites in supporting the growth and repair of neural structures.[2, 44, 45, 67] The ability of microbial metabolites to increase neurogenesis and modulate synaptic plasticity highlights their multifaceted impact on nervous system recovery.[20]

A variety of microbial metabolites have been reported to promote the neurogenesis and proliferation of glial cells. These metabolites interact with neural or glial progenitor cells, influencing their differentiation and proliferation. For example, enteric SCFAs at physiological concentrations were shown to promote the proliferation and mitosis of human neural progenitor cells and influence the expression of neurogenesis-related and apoptosis-related genes.[105] SCFAs can also modulate oligodendrocyte progenitor differentiation and myelination.[13] The effect of SCFAs on oligodendrocyte progenitors can be explained by the impact of SCFAs on microglia and astrocytes.[106] Another metabolite that can influence the proliferation of neural progenitor cells is CLA. CLA was shown to promote the neuronal differentiation of rat neural stem cells, increase the number of Tuj-1-positive cells, and induce the proliferation of neurospheres derived from rat neural progenitor cells.[60] Tryptophan metabolites produced by the gut microbiota, such as indole derivatives and kynurenine pathway metabolites, also

play crucial roles in neurogenesis and brain repair. For example, indole was found to enhance neurogenesis in the hippocampus of adult mice, as indicated by an increased number of doublecortin-expressing cells in the dentate gyrus. This stimulatory effect on adult neurogenesis is mediated through metabolic- and immune-linked AhR signaling.[107] Tryptophan-derived indole-3-lactic acid, produced by *Bifidobacterium*, was found to activate AhR and promote nerve growth factor (NGF)-induced neuronal differentiation via the ERK pathway.[26] The ERK signaling pathway is crucial for protein translational regulation, particularly in the context of long-term potentiation, which is essential for synaptic plasticity and memory formation. This, along with the observed increase in neurite outgrowth, indicates that indole-3-lactic acid may be a promising modulator of neuronal development and synaptic function.

Additionally, microbial metabolites can influence the production and release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), NGF and glial cell-derived neurotrophic factor.[108] These factors are critical for the survival, growth, and differentiation of neurons and play a significant role in brain repair and regeneration processes.[20] SCFAs, particularly butyrate, increase the expression of BDNF, a crucial factor for neuroplasticity, neuronal survival, and synaptic function.[17, 51] Lactate can also induce BDNF expression in the hippocampus through the upregulation of SIRT deacetylase.[7, 109] Furthermore, microbiota-derived indole-3-propionic acid was shown to induce the production of neuroprotective BDNF and NGF in neuronal cells by inhibiting the production of proinflammatory factors from microglia, which resulted in improved cognitive function and mental stress in elderly individuals.[45]

Microbial metabolites also play a significant role in axonal repair. Axons can be damaged by injury or disease, leading to loss of function and connectivity in the nervous system. SCFAs promote axonal regeneration by increasing the expression of genes involved in cytoskeletal dynamics and axonal growth.[108] Propionic acid, for example, upregulates the expression of growth-associated protein 43, a critical protein for axonal growth and regeneration. The antioxidative and neuroregenerative effects of propionate on Schwann cells and dorsal root ganglia are mediated by free fatty acid receptor 3-induced histone acetylase expression.[43] Lactic acid has also been shown to support axonal repair.[7] Lactate serves as an energy source for neurons and glial cells, providing the necessary ATP for the metabolic demands of axonal regeneration. It can also act as an astrocyte signaling molecule and regulate neuronal functions, including synaptic plasticity and axonal integrity.[110] Additionally, lactate can modulate the expression of genes involved in axonal growth and repair, further supporting the regeneration process.[111] Group B vitamins, which can be synthesized by various gut microorganisms, may also support axonal recovery and enhance neuronal function. Both demyelination and axonal deterioration are common in vitamin B deficiency as well as in many neurological diseases, including multiple sclerosis and Alzheimer's disease. Group B vitamins have been shown to enhance motor nerve regeneration and the recovery of muscle function in a rat model of peripheral nerve injury by reducing both Schwann cell decline and deterioration of the myelin sheath.[112] A recent study revealed that the gut metabolite indole-3-propionate promotes nerve regeneration and repair via an immune-mediated mechanism.[19] This metabolite, synthesized by *Clostridium sporogenes*, plays a crucial role in facilitating axonal regeneration. Administering indole-3-propionate after sciatic injury significantly enhances axonal regeneration, thereby accelerating the recovery of sensory function. In terms of mechanism, RNA sequencing analysis of sciatic dorsal root ganglia revealed that neutrophil chemotaxis plays a role in the regenerative effects induced by indole-3-propionic acid.[19]

Microbial metabolites also influence myelination. For example, SCFAs have been reported to mitigate demyelination and promote myelin regeneration in the corpus callosum.[13] Specifically, butyrate has been demonstrated to have a pro-regenerative effect on myelin in organotypic cerebellar slice cultures following lysolecithin-induced demyelination. Treatment with butyrate increased the number of mature $Olig2^+$ $CC\text{-}1^+$ oligodendrocytes.[113] The effect of butyrate on remyelination can be explained by its role in inhibiting histone deacetylases, as studies have shown that pharmacological inhibitors of histone deacetylases can similarly enhance remyelination.[13] Vitamin K2, which can be synthesized by the gut microbiota, also impacts the myelination of neurons. It is essential for the formation of sphingolipids, which are vital for neuronal growth and the myelination process within the nervous system.[68, 114]

Synaptogenesis is another critical aspect of nervous tissue regeneration influenced by gut microbiota metabolites.[7] SCFAs, particularly butyrate, can increase synaptogenesis and prevent dendritic spine loss and

neurite impairment. Butyrate treatment increases the percentage of mushroom-like spines and decreases the percentage of thin spines and stubby spines in the frontal cortex of obese mice.[115] Mushroom-like spines with large spine heads form strong synaptic connections and have the longest lifetime, making them crucial for long-term memory storage, synaptic plasticity, and cognitive processes. Another microbiota-derived metabolite, indole, has been shown to impact synaptic maturation. Mice treated with indole presented elevated levels of synaptic markers, such as postsynaptic density protein 95 and synaptophysin, indicating that indole enhances synaptogenesis.[107] An independent study of Alzheimer's disease confirmed that indoles can increase the expression of synaptic proteins such as postsynaptic density protein 95 and synapsin I, thereby improving synaptic plasticity and cognitive impairment.[71] In a mouse model of autism spectrum disorder, treatment with indole-3-propionic acid was shown to restore impaired inhibitory synaptic transmission in the hippocampal dentate gyrus via ERK1 signaling, resulting in improved social behavior.[116] It has also been reported that indole-3-propionic acid plays an important role in synaptic pruning by preventing excessive synapse elimination and synaptic impairment. This neuroprotective mechanism involves the inhibition of microglial activation mediated by AhR.[117]

The effects of the gut microbiota on neuroregenerative processes can also be mediated by the ability of the gut microbiota to synthesize neurotransmitters or neurotransmitter precursors, such as GABA, serotonin, 5-hydroxytryptophan, tryptamine, dopamine and norepinephrine. The gut microbiota has been reported to regulate the biosynthesis of host serotonin, also known as 5-HT. Indigenous spore-forming bacteria from mouse and human microbiota promote the production of 5-HT from colonic enterochromaffin cells.[8] 5-HT profoundly affects enteric neurons. By enhancing 5-HT production, the gut microbiota can influence synaptic signaling within the ENS, promoting better coordination of muscle contractions and overall GIT motility.[118] Furthermore, the modulation of serotonin levels by gut bacteria may contribute to the protection and regeneration of enteric neurons, supporting the resilience and adaptability of the ENS in response to physiological and pathological challenges.[119] Several bacterial genera, such as *Lactobacillus, Lactococcus, Bifidobacterium, Bacteroides and Akkermansia,* have been shown to produce GABA through the glutamate decarboxylase pathway.[9, 120] GABA-producing bacteria were shown to modulate sensory neuron activity in a rat model of visceral hypersensitivity, suggesting their potential as future treatments for recurrent abdominal pain and functional bowel disorders.[66, 121] The involvement of the GABAergic system in the pathogenesis of mood disorders is now widely acknowledged. The microbiota can alter the expression of GABA receptors in the brain, thereby reducing anxiety and depression.[46] Additionally, GABA plays a critical role in the ENS, regulates motility and mucosal function, and affects the gut–brain axis through the vagus nerve.[122] Dopamine and norepinephrine are another set of neurotransmitters whose metabolism is influenced by the gut microbiota.[66, 119, 123] They play pivotal roles in various aspects of brain function, including stress responses and motor control. However, the detailed mechanisms by which microbiota-derived dopamine and norepinephrine affect the CNS and ENS have not yet been fully investigated.

Therapeutic potential of gut microbiota metabolites

The nervous system has a limited ability to repair itself, making the development of strategies for neural regeneration and neuroprotection among the top priorities in neuroscience research. Effective treatments could significantly mitigate the long-term effects of neurological disorders, improve patient outcomes and ease economic strain on healthcare systems. Given the frequent occurrence of neurological disorders and often unsatisfactory clinical outcomes, improving recovery remains a significant challenge. In this context, the emerging role of gut microbiota metabolites in neuroregeneration and neuroprotection represents a promising and innovative frontier.[2] Accumulating evidence suggests that metabolites produced by the gut microbiota play crucial roles in neural repair processes by supporting neurogenesis, synaptogenesis, and axonal growth.[4, 19, 20, 24, 43, 45, 47, 67, 96, 107, 116, 117] For example, neurogenesis, which can be mediated by the gut microbiota through neuroactive compounds such as serotonin and GABA, is impaired in germ-free mice, which lack these microorganisms and consequently have fewer neurons in the ENS.[2] Moreover, microbial metabolites can promote regenerative processes through an immune-mediated mechanism. For example, microbiota-derived indole-3-propionic acid was shown to affect immune cells and modulate inflammatory responses, creating a supportive environment for the functional recovery of sensory axons.[19]

As research increasingly uncovers the profound effects of microbial metabolites on the nervous system, there is a surge of interest in exploring gut microbiota

metabolite-derived therapeutics for neuroprotection and regeneration. This has led to a heightened focus on the therapeutic potential of probiotics, postbiotics, and metabiotics (**Figure 3**). Overall, health-promoting microbial metabolites can be applied in a variety of ways. They can be produced in the GIT by live microorganisms (probiotics), or they can be introduced directly as bioactive compounds resulting from microbial metabolic processes (postbiotics).[124] Another approach involves the use of metabiotics, which collectively refer to microbial metabolites, constituents of nonlive microorganisms, and signaling molecules with well-defined chemical compositions.[125] Probiotics are considered a traditional method for influencing the microbiota–gut–brain axis, and numerous studies have shown the potential of probiotics for alleviating neurodegenerative disorders, as well as promoting neurogenesis and synaptogenesis.[46, 67, 125] The advantages of using probiotics include their safety, nonpathogenic nature, and ability to interact directly with the gut microbiota via quorum sensing. For probiotics to generate health-promoting compounds effectively, they must survive the harsh conditions of the GIT, such as low pH and high concentrations of bile salts, and demonstrate a strong ability to adhere to intestinal epithelial cells. Moreover, because each person has a distinct gut microbiota profile, dietary habits, and geographical influences, probiotics can produce different metabolites in varying amounts when used by different individuals. This variability can lead to heterogeneous effects on the microbiota–gut–brain axis among different people. Another limitation of probiotics is their potential user-unfriendliness for immunocompromised individuals, which can restrict

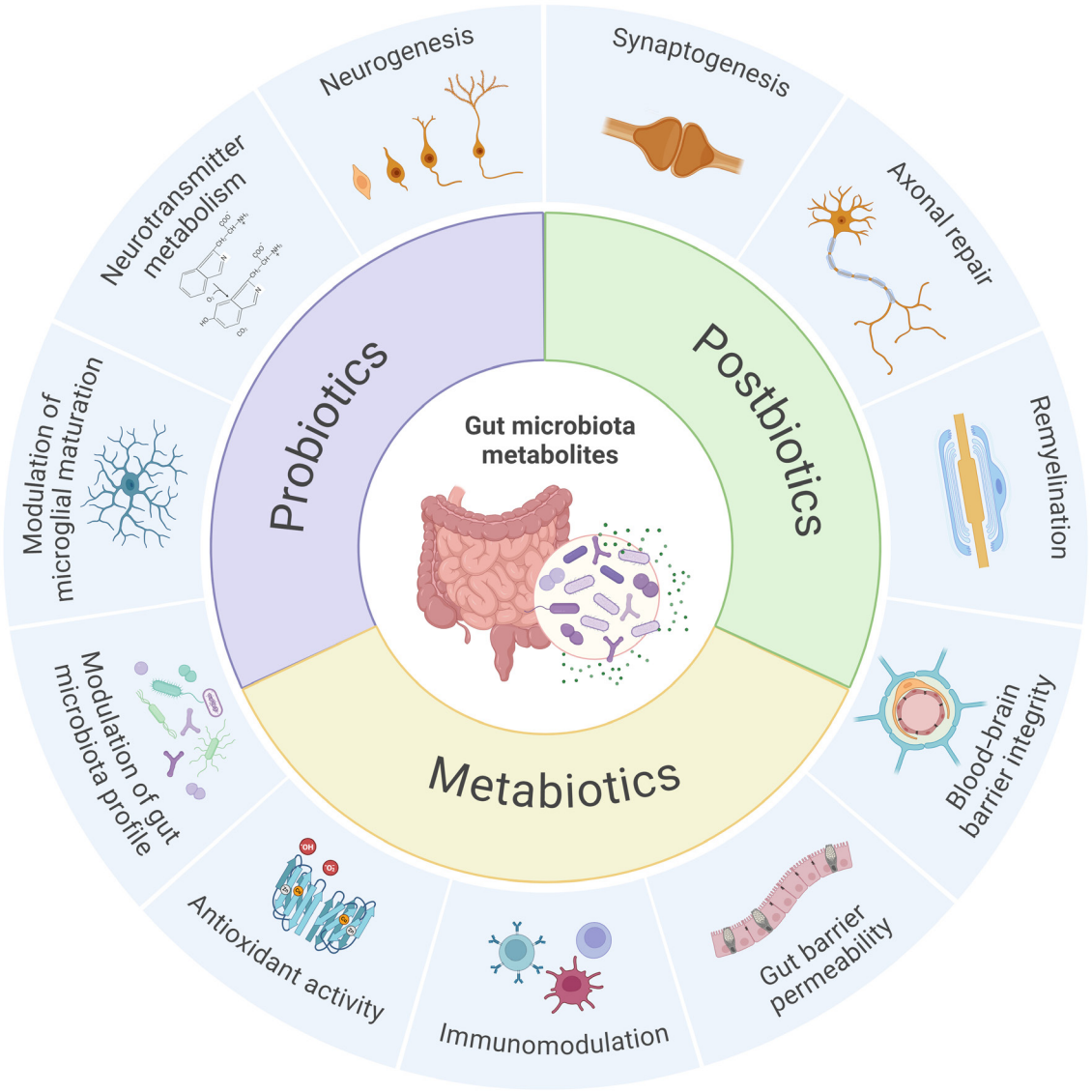

Figure 3: Schematic illustration of the therapeutic potential of gut microbiota metabolites
Note: Created with BioRender.com.

their use in therapies.[126] Alternative biotherapeutic products, such as postbiotics and metabiotics, which consist of microbial metabolites and microorganism-derived cell components, may offer benefits over probiotics. They tend to be safer for sensitive populations, including neonates, young children, immunocompromised individuals, and critically ill patients, and are more resistant to the harsh conditions of the GIT.[127] Furthermore, controlling the production of metabolites–both in terms of quality and quantity–is more straightforward under defined fermentation conditions with specific culture environments than in the host gut environment, ensuring more predictable, dose-specific physiological effects. Postbiotics and metabiotics also provide improved stability and transportability, which extends shelf-life and simplifies packaging.[125]

Although many studies have shown the potential of microbial metabolites to promote neuroregenerative processes, the effectiveness and strategies of microbial metabolite therapies remain debatable, and more studies and large-scale clinical trials are needed. Moreover, it is essential to thoroughly investigate both the well-documented and potential species and possibly strains of human gut microbiota that could be used for the production of health-promoting metabolites. Future research should focus on identifying and characterizing the ability of these microorganisms to synthesize bioactive compounds, as well as understanding their functional roles within the microbiota–gut–brain axis. This study will help to uncover new strategies for developing targeted probiotic, postbiotic or metabiotic interventions, ultimately leading to advancements in maintaining nervous system health and broader therapeutic applications.

Limitations

This review has several limitations. Because this is a narrative review, it does not provide a systematic quantitative evaluation of the quality or relevance of all included studies, leading to potential selection bias and incomplete coverage of the literature. Moreover, the review focuses predominantly on bacterial metabolites, largely owing to the limited research available on fungal and archaeal metabolites. This emphasis may overshadow the potential impact of these less-studied metabolites on the microbiota–gut–brain axis, given the diverse nature of the gut microbiota. Given that this review addresses a wide array of microbial metabolites, the discussion of the mechanisms of action for each specific gut microbiota metabolite is limited in depth. Further research and clinical trials are needed before possibilities for evidence-based therapeutic applications of gut microbiota metabolites can be identified.

Conclusion and Future Directions

Gut microbiota metabolites play crucial roles in maintaining the functional balance of the microbiota–gut–brain axis, thus offering neuroprotection and promoting regeneration of nervous tissue. Research in this field continues, providing more information on specific mechanisms and approaches to repair neural tissue through microbiota modulation and the direct use of certain metabolites. Despite the significant therapeutic potential of these metabolites, further investigations are needed for evidence-based clinical applications. Key research directions include identifying probiotic strains that produce health-promoting metabolites and understanding the specific mechanisms through which the microbiota influences the nervous system. The challenge is elucidating the mechanisms by which microbial metabolites affect brain function, which stems from the unclear rate at which some microbial molecules are transported to the brain. It is also difficult to differentiate the direct effects of microbial metabolites on CNS function from those of indirect communication pathways, such as immunological pathways, or via the vagus nerve, which can confound *in vivo* studies. Therefore, further research is crucial to elucidate the mechanisms of absorption and transport of microbial metabolites and neurotransmitters from the gut to the brain. Additionally, exploring the roles of fungal and archaeal metabolites in the microbiota–gut–brain axis is important. Comprehensive experimental and clinical studies are needed to validate the protective effects of microbiota metabolites in neurological disorders.

Author contributions

Conceptualization, writing – original draft, and visualization: OK; conceptualization, writing – review & editing, and supervision: IL; conceptualization, writing – review & editing, and supervision: GS. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

Not applicable.

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