Review Article

Neurochemical Signaling Molecules in Gut–Brain Axis: Microbial Metabolites and Therapeutic Implications

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ABSTRACT

The gut–brain axis is a bidirectional communication network linking the gastrointestinal tract and central nervous system and is significantly influenced by the gut microbiota. Emerging evidence indicates that microbial dysbiosis alters neurodevelopment, neurotransmission, and behavior, contributing to psychiatric and neurodegenerative disorders, such as depression, autism, Parkinson's disease, and Alzheimer's disease. Key mediators of this crosstalk are microbial metabolites and neuroactive compounds including γ-aminobutyric acid (GABA), short-chain fatty acids (SCFAs), indole derivatives, and tryptophan metabolites. These bioactive molecules modulate brain function by affecting neuronal signaling, neurotransmitter balance, immune responses, and intestinal barrier integrity. This review emphasizes the chemical and functional roles of these compounds in mediating gut–brain communication. Understanding their structure–activity relationships offer novel insights into therapeutic approaches involving probiotics, prebiotics, dietary modulation, and microbial metabolite targeting. Rather than addressing all disorders, this review focuses on the molecular mechanisms underlying gut-derived neurochemical signaling and its relevance to brain health, highlighting promising strategies for managing neuropsychiatric conditions through microbiota modulation.

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Content

1. Introduction

Microbiota refers to a specific group of microorganisms living in a particular environment, while "commensals" refer to those that colonize a host without causing disease. Advancements in omics technologies, such as metagenomics and culturomics, have significantly enhanced the diversity of human microbiota [1].

The gut microbiota constitutes a complex ecosystem that supports a diverse and abundant collection of bacteria that co-evolve in a mutually beneficial interaction within a human host. Additionally, the gut microbiome encapsulates all genetic traits of gut bacteria that are intimately associated with the host's state of health. Furthermore, the microbiome is the major "virtual organ" of the body because the human gastrointestinal system is a rich habitat with approximately 100 trillion bacterial cells [2].

As a result, the microbiome regulates and changes the fitness, phenotype, and health of the host. Known as an imbalance in this intricate ecosystem, dysbiosis causes different human diseases that can appear at any level of the physiological system [3].

Intestinal dysbiosis is increasingly linked to the pathogenesis of both gut-related and extraintestinal diseases, even though the term "dysbiosis" is a general one that has recently been adopted as a mental shortcut [4].

However, the intricate makeup of the gut microbiota is unique to each organism and plays a major role in determining an individual's overall health as well as the negative consequences that arise from the overabundance of pathogenic microorganisms, or "pathobionts" [5].

Furthermore, the vital physiological processes of the host are directly affected by the gut microbiota, which also influences and modulates immune system activity, intestinal

barrier integrity, metabolic and nutritional homeostasis, and cerebral activity [6].

Gut microbiota play a crucial role in neurological and psychiatric disorders, and studies have revealed changes in gut microbiota composition in conditions including depression, anxiety, autism spectrum disorder (ASD), schizophrenia, epilepsy, and Parkinson's disease (PD). The cause-effect relationship between gut microbiota dysbiosis and specific diseases remains unclear, with it potentially being a combination of both [7,8].

Possible thematic/functional connections between bidirectional gut-brain communication pathways and pathological changes in gut microbiota, with a focus on the possible contributions of gut dysbiosis to the pathophysiology of mental diseases. This study investigated the potential relationship between PD and pathophysiological events, suggesting that these events may contribute to the development and persistence of other mental disorders [9].

This study explored the mechanisms of pathogenic microorganisms and their microbiota in chronic neurologic and psychiatric disorders, focusing on therapeutic strategies and future perspectives.

2. Disruption of the Microbiome in Neurodegenerative Diseases

Various brain diseases, such as multiple sclerosis (MS), PD, and ASD, may be caused by modifying the interactions of the microbiota, stomach, and brain (**Figure 1**) [10-13].

There is disagreement over the significance of intestinal dysbiosis in the etiology of neurological disorders, and there is currently a lack of information regarding the underlying mechanisms of the fault. Preclinical data have demonstrated the significance of experimentation with autoimmune encephalomyelitis (EAE) and its role in the microbiome. In both inducible [14] and spontaneous models [15], EAE in GF mice was neither present nor markedly diminished. Additionally, mice with GF colonized with bacteria restored EAE susceptibility [15], as opposed to the depletion of commensal microbiota by oral antibiotics, which restored EAE severity in comparison to control animals administered intraperitoneal antibiotics or phosphate-buffered saline treatment [16].

Furthermore, unlike wild-type mice, amyotrophic lateral sclerosis (ALS) transgenic mice showed a considerable reduction in butyrate-producing bacteria (*Butyrivibrio fibrisolvens*), *Escherichia coli*, and *Firmicus sp*., indicating dysbiosis [14]. Prevotellaceae was less prevalent in in-patient samples of stool with PD in comparison to controls in investigations on adults [16], although it was positively correlated with the degree of postural instability, and gait difficulties symptoms were linked with the presence of Enterobacteriaceae. Unrelated to constipation, a higher level of urinary indoxyl sulfate had been developed when the illness first appeared and may therefore be involved in PD pathogenesis [17].

Studies on MS patients in humans have also been conducted; despite the small sample sizes, these studies often discovered abnormalities in the microbiota that may be involved during the inflammatory stage of the disease [18].

ASD is a major topic of research in children. Although researchers generally agree on several variations between children with ASD and their healthy siblings or unrelated controls in terms of the composition of their microbiota [19], investigations occasionally produced inconsistent findings regarding the type or quantity of microorganisms involved [20].

Using pyrosequencing, 33 children with ASD were found to have different fecal microbiota. and discovered that, compared to controls, patients with ASD had lower concentrations of a combination of Firmicutes and Actinobacteria (particularly Bifidobacterium), and higher proportions of Proteobacteria and Bacteroidetes [21].

A considerably larger number of *Ruminococcus torques*, *Sutterella*, *Bacteroides vulgatus*, and *Desulfovibrio* species has been reported [22,23], which was also abnormally prevalent in the gut microbiome of youngsters with ASD [24]. Furthermore, Coprococcus, Prevotella, and unidentified Veillonellaceae were found at much lower concentrations than in healthy controls, and these alterations were associated with the severity of ASD symptoms in children

with gastrointestinal troubled ASD children [24].
Furthermore, various studies have shown that there are more types of *Clostridium* in the feces of children with autism [25,26].
Clostridia are involved in the ASD development, as children with ASD who received vancomycin orally saw a reversal of their normal symptoms. It is possible that these microorganisms contribute to the development of ASD because this antibiotic's spectrum of action includes gram-positive bacteria such as *Clostridium* and because discontinuing vancomycin resulted in a return of ASD symptoms [27].

3. Factors Relating to the CNS and Microbiota

3.1. Antibiotics usage

Antibiotics selectively alter gut microbiome Mice receiving oral antibiotic preconditioning were less susceptible to autoimmune diseases, including EAE. According to a previous study [16,28], improvement in EAE was linked to decreased Systemic Treg and Breg activation and elevated IL-13, IL-10, IFNc, and IL-17.
The hygiene hypothesis is supported by the fact that antibiotics shift the Th1/Th2 balance in favor of Th2. In the course of treating EAE with antibiotics, IFNc and IL-17 pro-inflammatory cytokines were also shown to be lowered, according to a previous study [29].
Antibiotics did not increase iNKT cells but were necessary for defense against EAE. These EAE investigations used different antibiotic drugs, which would have produced various gut microbiome profiles and explained the diversity of the immunological responses. The positive effects of antibiotic treatment on neurobehavioral disorders have been supported by recent studies. Children with autism, who had regressive onset, benefited temporarily from antibiotic treatment because it decreased in mice, stress reactions, and increased exploratory behavior. The alteration of CNS indicators, such as BDNF synthesis in the hippocampus and luminal lipopolysaccharides (LPS) concentration (and subsequently a potential reduction in chronic inflammation) may be the underlying mechanisms [30-32].

3.2. Microbiota-derived products and their chemical basis

The gut microbiota synthesizes various neuroactive compounds that exert profound effects on the brain. The most notable features are the following:

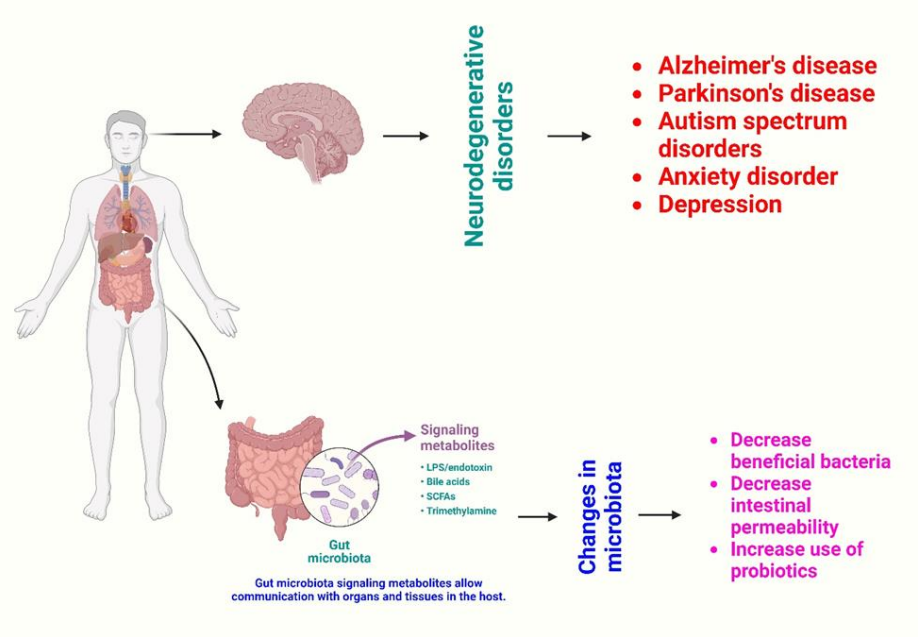

Figure 1. Interaction between gut microbiota and neurodegenerative disorders

GABA (γ-aminobutyric acid)

GABA is a non-protein amino acid characterized by a four-carbon backbone, with a terminal carboxylic acid group (–COOH) and an amino group ($–NH_2$) located at the γ-position. It primarily functions as an inhibitory neurotransmitter in the central nervous system (CNS).

At the receptor level, GABA interacts with both the GABA-A and GABA-B receptors, with the former being a ligand-gated chloride ion channel. Upon binding, the amino group of GABA forms hydrogen bonds with polar amino acid residues, such as tyrosine or serine, while the carboxyl group engages in ionic interactions with basic residues, such as arginine or lysine, within the receptor-binding pocket. This precise arrangement facilitates the opening of the chloride channel, leading to Cl^- influx, neuronal hyperpolarization, and reduced the excitatory signaling. Many Lactobacillus and Bifidobacterium species produce GABA via glutamate decarboxylation, and the resulting metabolites may affect host mood and anxiety by modulating signaling along the gut–brain axis.

Short-chain fatty acids (SCFAs)

SCFAs, which include acetate (C_2), propionate (C_3), and butyrate (C_4), are saturated aliphatic carboxylic acids produced by bacterial fermentation of dietary fibers. These metabolites exert their effects through G-protein-coupled receptors such as GPR41 (also known as FFAR3) and GPR43 (FFAR2). The carboxyl group of SCFAs is critical for receptor activation because it forms electrostatic interactions with the conserved arginine residues at the receptor-binding site. Butyrate, in particular, demonstrates high affinity due to the optimal length of its hydrophobic tail, allowing the additional van der Waals interactions that stabilize the receptor–ligand complex. Beyond receptor binding, SCFAs function as histone deacetylase (HDAC) inhibitors, with butyrate being the most potent. This activity results in epigenetic modifications that alter chromatin structure and gene expression, thereby affecting some processes such as neuroinflammation, microglial activation, and synaptic plasticity in the central nervous system.

Indole and indole derivatives

Indole is an aromatic heterocyclic compound formed by bacterial metabolism of tryptophan via tryptophanase (**Figure 2**).
Structurally, it consists of a fused bicyclic system containing a benzene ring and nitrogen-containing pyrrole ring, which enables strong π–π interactions and hydrogen bonding. Indole and its derivatives, indole-3-acetic acid and indole-3-aldehyde, interact with difference host receptors, including aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and serotonin (5-HT) receptors. In the case of AhR, the planar aromatic structure of indole fits tightly into the hydrophobic ligand-binding pocket of the receptor, where it establishes stacking interactions with aromatic residues, ultimately triggering transcriptional programs that regulate intestinal immunity and blood–brain barrier function. Furthermore, indoles affect serotonin biosynthesis indirectly by modulating the availability of tryptophan and directly by acting on enterochromaffin cells via receptor-mediated pathways. These interactions contribute significantly to maintaining intestinal barrier integrity and regulating neuroendocrine signaling.

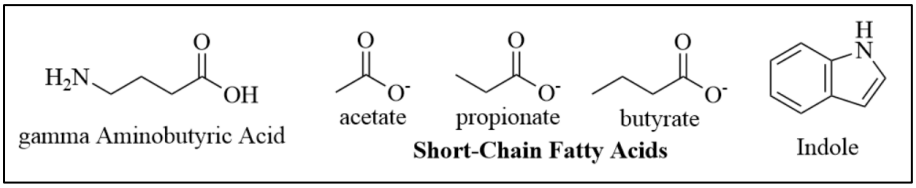

Figure 2. The structures of neuroactive compounds synthesized by gut microbiota

3.3. Microbiota-derived products

Products made from bacteria are frequently efficient components of the microbiota-gut-CNS communication chain.

This is particularly clear Regarding *B. fragilis* capsular PSA, which can perform the same tasks as its parent organism B. fragilis for the stimulation of intestinal sensory neurons and anti-inflammatory effects in EAE. A unique zwitterion known as PSA is also known as a commensal symbiosis factor [33,34].
Luminal extracellular ATP and LPS, which are produced by commensals, promote chronic inflammation, which aids in the etiology of neuroimmune and neuropsychiatric conditions. The co-metabolites and metabolites generated by the microbiota are essential mediators of microbiota-gut-CNS communication. An array of neuroactive chemicals are produced by commensals. For instance, GABA, an inhibitory neurotransmitter, can be produced by *Lactobacillus* and *Bifidobacterium* species [35].
It is still unknown whether probiotic effects on neuropsychiatric diseases entail neuro-active metabolites. The byproducts of microbiota metabolism are fatty acids called SCFAs, which have aliphatic tails with two to six carbons. Few studies have focused on SCFAs' effects of SCFAs on CNS diseases despite the fact that they have been demonstrated to be significant immune regulators [36].

3.4. Microbiota composition

Several techniques can be employed to determine how microbiota composition affects CNS diseases, including the microbiota caused by infection disruption, research using GF mice mono-colonized, metagenomic analysis, SPF and gnotobiotic mice, and methods including the 16S rRNA profiling method with microbial microarray. Furthermore, by analyzing the metabolites and co-metabolites of the microbiome, compositional changes in the serum antibody titers of the microbiota can be indirectly reflected through food items and the microbiome. There have been few attempts to identify enterotypes that are specific to particular diseases because enterotype research is still in its infancy [37] discovered two ET1 and ET2 mice enterotypes showed striking similarities, to different human enterotypes of Ruminococcus and Bacteroides. Fecal calprotectin, a biochemical marker of IBD, was found at higher concentrations in ET2 mice. However, a clear connection between enterotypes and CNS diseases has not been discovered yet. For instance, there are both positive and negative findings regarding the association between Bacteroides enterotype and autism [24,38].

3.5. Hygiene

According to hygiene theory, T helper 2 (Th2)-mediated allergic disorders are more susceptible when children are not exposed to infectious diseases, parasites, and commensals. However, there is also a relationship between better sanitation and an increase in autoimmune disorders mediated by T helper 1 (Th1), including T1 diabetes and multiple sclerosis [39].
The Th1 response, which is mediated by the sign cytokine IFNc, targets intracellular microorganisms, while the Th2 response, which is mediated by the hallmark cytokines IL-4 and IL-13, targets helminths and allergens. Therefore, abnormal immunological development could indicate a relationship between hygiene and immune-mediated CNS diseases. Although the results from human MS contradicted the hygiene concept, lower Th1, Th17, and B cell responses and lower EAE symptoms have been observed in GF mice [14,15]. The many etiologies of human MS and the inherent variations between mouse GF disease and the human hygiene state may help to explain this gap. GF syndrome is associated with neurobehavioral abnormalities in mouse models. Elevated levels of neurotransmitters in the plasma are associated with decreased BDNF levels and increased HPA axis responses to total sterility. Increased stress levels and cognitive impairment have been observed in GF animals [40,41].
However, some investigations have found that the GF state is anxiolytic and can relieve anxiety, which is associated with lower neurotransmitter receptor levels [42,43].

3.6. Diet

Dietary habits may modify the gut microbiota by changing nutrient availability. Recent research suggests that dietary changes may affect the diversity of gut microbes. Lower microbiome richness has been linked to metabolic dysfunction and low-grade inflammation, and has been identified as being less healthy. High-fiber dietary supplements can increase the microbiome diversity [44,45].
Neuroinflammation during EAE may be accelerated by unhealthy dietary patterns rich in fat or salt [46,47].
Depending on immunological health, a Western-style diet may have a deleterious impact on anxiety-like behavior and memory [48].
Depression may be reduced by increased PUPA supplementation [49].

4. Neurodegenerative and Psychiatric Disorders and Intestinal Microbiome

The relationships among neurodegenerative disorders, psychiatric disorders, and the intestinal microbiome are discussed below (**Figure 3**).

4.1. Autism spectrum disorder (ASD)

One of the most severe and devastating neurodevelopmental conditions is ASD, which is linked to the makeup of GI microbiota. According to the CDC's Autism and Developmental Disabilities Monitoring Network (ADDM), one in 44 children in the US has an ASD diagnosis [50,51].
Unusual behavior, challenges with interaction and relationship development, and sensitivity to sensory impulses, either hypo- or hyper-in the environment, are characteristics of ASD [52].
Azouz *et al.* [53] found that 82.5% of 40 children with autism aged 3-12 years displayed gastrointestinal symptoms. Additionally, dysbiosis associated with the Bacteroides to Firmicutes Ratio as well as the number of individuals with ASD showed the phyla Firmicutes, Bacteroidetes, Fusobacteria, and Verrucomicrobia [54].
The same study found that alterations also affected the levels of SCFAs and volatile organic compounds, such as indole, a tryptophan metabolite, and a precursor to serotonin and melatonin.

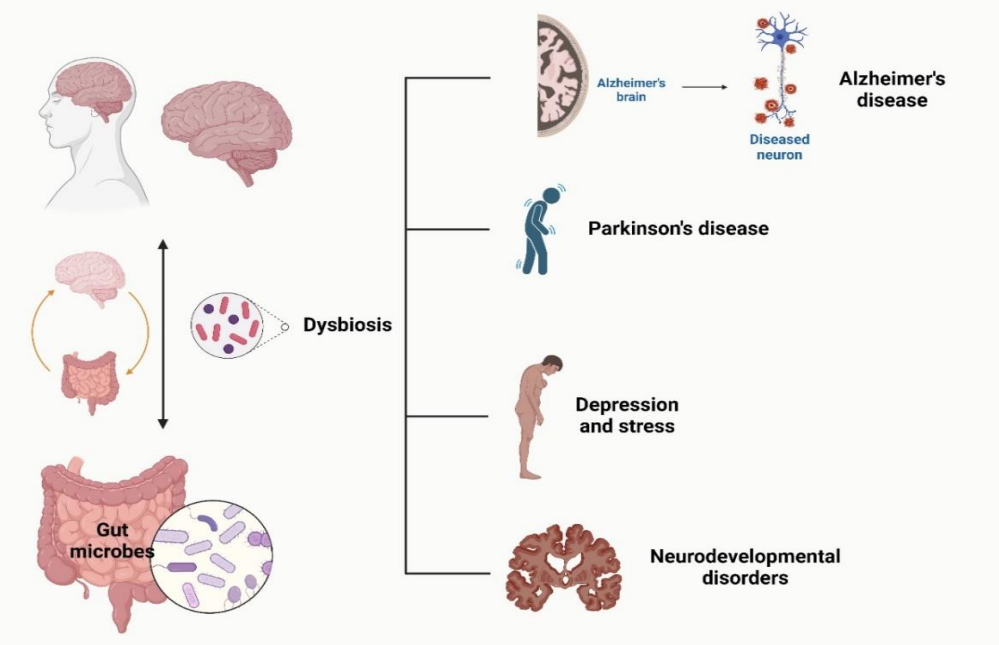

Figure 3. The microbiome-gut-brain axis research reveals a bidirectional communication between gut microbiota and the central nervous system, affecting neurological and psychiatric health. Dysbiosis, imbalance in gut microbial composition, is linked to conditions such as Alzheimer's, Parkinson's, depression, and anxiety

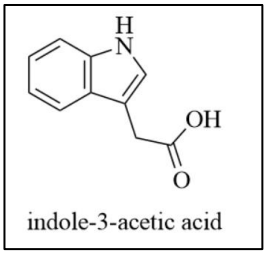

Figure 4. Chemical structure of indole-3-acetic acid (IAA), a microbiota-derived tryptophan metabolite

However, because of how tailored nutrition plans or antibiotic therapy may affect people with ASD [55], these data should be evaluated with caution. Elevated indole levels and decreased SCFA production have been reported in ASD. Chemical derivatives of indole, such as indole-3-acetic acid (**Figure 4**), interfere with the neurotransmitter pathways.
The aromatic ring systems of these molecules allow them to interact with CNS receptors, thereby affecting neurodevelopment.

4.2. Bipolar disorder

Recurrent and persistent bipolar disorder (BD), marked by recurrent hypermanic episodes or ensuing depressed symptom periods, shares a few signs of SCZ and is a dangerous mental disease [56,57].
Between 2017 and 2019, it was anticipated that BD affected 46 million people worldwide, including New Zealanders, making up the largest proportion [58,59].
Although much remains to be learned about the pathophysiology of BD, changes in tryptophan catabolites (TRYCATs), neuroregulatory tryptophan stress (O&NS), and immune-inflammatory activities have been suggested as the causes and progression of BD [60].
TRYCATs in BD patients and healthy controls were compared using a meta-analysis [61] and were shown to be lower in the CSF or serum/plasma of bodily fluids. Additionally, the effect of the gut flora on the onset of BD should be considered. The gut microbiota of patients with BD showed a correlation between GM dysbiosis and disease development [62].
Increased Coriobacteraceae concentrations have been linked to higher cholesterol levels, per research focusing on the variety of the intestinal microbiome [63], while increased Lactobacilli concentrations have been linked to the emergence of obesity in BD patients [64].
Diseases can also be linked to decreased levels of the innate gut bacterium Faecalibacterium [65].
Four times fewer Clostridiaceae were present during the fermentation of carbohydrates, resulting in SCFA production in BD patients compared to the control group [66-68].
Tryptophan, an essential amino acid, is the precursor of serotonin and kynurenine. Dysregulation of this pathway leads to overproduction of kynurenic acid, a glutamate receptor antagonist (**Figure 5**).

4.3. Attention-deficit hyperactivity disorder

Worldwide, 6 million children suffer from attention deficit hyperactivity disorder (ADHD). between the ages of 3 and 17 years is a prevalent neurodevelopmental disorder [69].

The primary etiological components of this condition are thought to be dopamine and serotonin transmitter genes as well as DRD4 and DRD5 dopamine receptor genes [70].

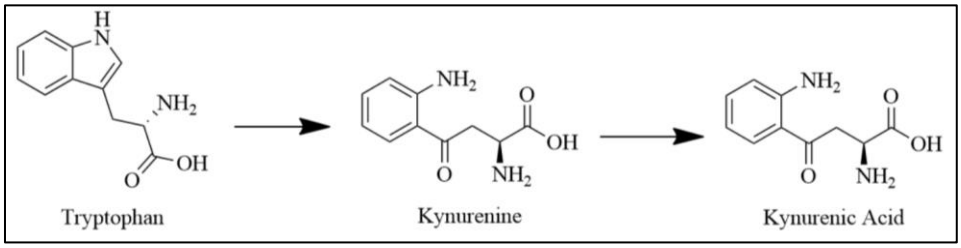

Figure 5. The kynurenic acid pathway

The link between the gut, brain, and microbiota is supported by a growing body of research [71,72].

On the other hand, Wang *et al.*'s [73] meta-analysis that examined the gut microbiota and ADHD did not find any appreciable variations, except for the greater abundance of Blautia in patients with ADHD than in healthy controls at the phylum or family levels. These microbial species control bio-transformation as well as metabolic and inflammatory diseases [74].

Future studies that focus on the relationship between ADHD and the microbiota, gut, and brain axis should be conducted, including a broader, more diverse study population [75].

Probiotic supplementation in utero may reduce the risk of neuropsychiatric disease. According to Pärtty *et al.* [76], early *Lactobacillus rhamnosus* GG supplementation with LGG may reduce the risk of ADHD. *L. rhamonsus* controls the expression of central GABA receptors and vagus-nerve-mediated emotional behavior in mice [77].

Additionally, it is critical to consider how dietary habits affect patients with ADHD. Considering that food contains artificial colorants, it is vital to eliminate such substances from the diet of ADHD patients to reduce their hyperactive behavior [78].

Additionally, it is important to consume omega-3 PUFAs, especially the essential fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are both necessary for optimal membrane fluidity, neurotransmission, and receptor function [79].

A diet high in omega-3 PUFAs resulted in individuals with less impulsivity and better concentration in a study employing male animals as ADHD models [80].

4.4. Schizophrenia

A multifactorial disease called schizophrenia involves cognitive, vocational, and emotional problems [81]. Adults with SCZ are susceptible to early mortality due to cardiovascular, metabolic, and infectious diseases. The average potential life loss for patients with SCZ in the United States is pegged at 28.5 years [82].

Owen *et al.* [83] found that SCZ exhibited three distinct characteristics that were classified as well as positive symptoms (delusions and a loss of reality), negative symptoms (a decrease in desire and withdrawal), and cognitive impairment (less efficient than controls) are all possible indicators of schizophrenia. Researchers have also attempted to elucidate SCZ etiopathogenesis using biochemical and neuroimaging techniques. Thus far, it has been feasible to identify certain dependencies between different neurotransmitters in different systems, which may, at least in part, explain how the clinical signs of SCZ develop. The involvement of dopamine appears to be the most important [84], even though dopamine only has a very slight influence on this disease. Additionally, SCZ sources should be discovered in connection with the other neurotransmitters [85-87].

Alarmins are a class of host peptides and proteins that stimulate various signaling pathways. This results in the emergence of numerous inflammatory conditions caused by infections or infertility, suggesting a relationship between immunological mechanisms and SCZ's etiology of SCZ. A growing body of evidence supports an important function of the glutamatergic system. DAOA, an inhibitor of d-serine amino acid oxidase, and the G72 gene on chromosome 13q33, the latter of which functions as an amino acid oxidase activator, are primarily involved in this process, which activates NMDA receptors and is encoded by the neuregulin 1 gene on chromosome 8p12 [88].

The discovery of these genes suggests that the glutamatergic system plays a role in this process, as well as the neurodevelopmental theory of SCZ [89].

A growing body of evidence suggests that both pathways are regulated by kynurenic acid (KYNA) [90].

The NMDA and kainic acid receptors, as well as the AMPA receptor and All of the NMDA receptor complex excitatory amino acid ionotropic receptors, except for the strychnine-independent glycine site, are ionotropic and non-selective antagonists of KYNA. Patients with SCZ had higher levels of KYNA in their CSF. KYNA's possible function in the physiology and pathophysiology of the CNS is increasingly understood as a result of studies on this

substance. However, it has not been clearly stated how KYNA affects CNS function. Therefore, the clinical characteristics of many diseases. However, large variations in KYNA concentrations in healthy and ill individuals suggest that this molecule plays a role in the growth of neurological and mental disorders [91].

The structure of kynurenic acid enables the antagonism of NMDA receptors, impairing cognitive function. Structural features include an aromatic ring and carboxylic acid, which are critical for binding to glutamatergic targets.

5. Changes in Microbiota have Effects on Neurodegenerative Diseases

Gut microorganisms produce neurotransmitters, interact with the CNS, and affect neurological health. Additionally, they control how people behave and feel [92,93].

In some cases, the initiation and progression of NDs and CNS malignancies are significantly influenced by the interaction of gut microbiota with the CNS [94].

Additionally, because the host's microbiota and gut have a symbiotic relationship, disrupting this dynamic interaction has a detrimental effect on the health of the host, including cortical injury [95,96].

Although ENS failure is the cause of neurodegeneration, numerous clinical studies have demonstrated that people with neurodegenerative diseases also experience gut and microbial dysbiosis [96,97].

Changes in the gut microbiota, which are influenced by genetic or environmental factors (such as dietary and lifestyle choices, the use of antibiotics, location, etc.), are thought to have an effect on moderate to severe neurological conditions such as depression, anxiety, ASD, AD, PD, schizophrenia, MS, and epilepsy [98-100].

Nervous anorexia is a severe obsessive eating disorder characterized by unrelenting self-starvation. It has a high death and morbidity rate and is associated with lower recovery rates, primarily due to increased gastrointestinal instability [101,102].

5.1. Alzheimer's disease

The most common cause of dementia in aging cultures is AD, which causes a progressive and permanent decrease in cognitive ability. The AD pathophysiology is defined by the intracellular buildup of neurofibrillary tangles composed of hyperphosphorylated -protein and extracellular plaques composed of amyloid-β(Aβ) peptides [103].

Deposits are hypothesized to be associated with neuroinflammation and oxidative stress in the brain, which causes synapse loss and neuronal death. Its production and buildup often start around the age of 40, but it may take more than 20 years to cause cognitive impairment. Consequently, once it becomes clinically evident, AD progression is too far to be treated [104].

This finding emphasizes the significance of adopting dietary and lifestyle behaviors that prevent and postpone the onset of AD. Neurodegenerative disorders typically manifest in old age when the composition of the gut microbiota is influenced by a variety of factors, including poor diet and drug use. The development of AD is associated with a physiological cascade that starts with heightened gut barrier permeability and immune activation and progresses to systemic inflammation over time, which may further compromise the blood-brain barrier (BBB) and boost neuroinflammation, neural injury, and ultimately neurodegeneration [105].

A large number of amyloids, LPS, and other microbial byproducts are released into the surrounding environment as a result of age-related changes in the composition of the gut microbiota, specifically a decrease in diversity and stability. These secondary metabolites may be associated with a gut mucosal condition that is chronically inflammatory as well as with gut barrier degradation. Affected signaling pathways that result in the generation of pro-inflammatory cytokines, some of which are associated with the AD pathophysiology, are affected by the absorption of these substances [106].

Nevertheless, metformin is linked to medical therapies utilized by therapists to lessen and avoid AD patients' symptomatology [107-109].

A substance with a metabolic signature, particularly insulin resistance [109].
According to clinical data on gut dysbiosis in AD, elderly patients with cognitive impairment and brain amyloidosis may have peripheral inflammation due to an increased abundance of pro-inflammatory *Escherichia/Shigella* gut microbiota taxon and decreased abundance of anti-inflammatory *Eubacterium rectale* [110].
Through genus-wide differences in bacterial abundance, it was possible to detect changes to the gut microbiota in fecal samples from age- and sex-matched individuals as well [111].
Participants with AD had lower concentrations of Firmicutes and Bifidobacterium, and higher concentrations of Bacteroides in their microbiomes. It is interesting to note that certain correlations are caused by LPS and AD pathogenesis, and are related to the outer membrane of gram-negative bacteria. In the rat brain, LPS facilitates the development of amyloid-like plaques, and additional studies on the human brain suggest that LPS in combination with other variables may result in AD neuropathology [112].
In conclusion, data from both animal and human studies support the hypothesis that gut dysbiosis is associated with microglial activation during the onset of AD, and boosts the development of innovative AD therapeutic approaches based on gut microbiota remodeling [113].
Since hereditary variables are still unavoidable, managing indirect risk factors, such as lifestyle choices, may alter how AD develops. In food and lifestyle recommendations for the prevention of AD, certain controllable risk factors have been outlined [108], including regular physical activity, regular sleep schedules, and regular mental activities that foster new learning. The effectiveness of meditation in enhancing cognitive function, stress reduction, sleep, emotional regulation, and related physiological outcomes has only been weakly supported by clinical research. The effectiveness of meditation as a therapeutic intervention must be studied in larger, more meticulous randomized controlled studies [114].
However, the practice of meditation may prevent age-related anatomical and functional brain alterations in seasoned older meditators [115].
Lipopolysaccharides (LPS), particularly the lipid A moiety, initiate inflammation and disrupt the BBB. This amphipathic molecular structure facilitates the binding of immune receptors.

5.2. Dementia

Memory issues, personality changes, decline in thinking and social skills, and impaired reasoning are just a few signs that define dementia as a psychiatric disorder. Patients, families, and society are affected by these symptoms in physical, psychological, social, and economic ways. Age-related dementia affects 50 million elderly people worldwide, and 130 million more people are anticipated by the year 2105 [116].
Neuropsychiatric symptoms, often known as behavioral and psychological dementia symptoms, include changes in sleep or appetite, agitation, aberrant motor behavior, anxiety, exhilaration, irritability, depression, apathy, disinhibition, and depression [117].
Numerous studies have shown that AD-related neurodegeneration in older people is the main contributor to dementia risk; approximately 60-70% of patients go on to develop dementia. Cardiovascular and cerebrovascular diseases, including heart disease, stroke, brain infarcts, and cerebral microvascular lesions, are the second leading causes of dementia [116, 118, 119].
To analyze and prevent cognitive decline and dementia in elderly adults, randomized clinical trials have been conducted with the goal of lowering the main risk factors, such as poor diet, alcoholism, smoking, diabetes mellitus, depression, genetic factors, familial aggregation, hypertension, and obesity [116]. Controlling and modulating microbiota can be crucial in preventing dementia because it is now known that metabolic and inflammatory pathways play a crucial role in neurodegeneration. Reduction or stimulation of risk factors for cognitive loss, such as dementia, depends directly on the amount of Bacteroides present [111,120]. The most researched probiotic strains include *Lactobacillus*,

Bifidobacterium, and *Streptococcus*, which have a variety of positive effects on human health, including enhancing the host immune system, acting as a barrier to pathogenic organisms by adhering, reestablishing the microbiota, restoring health, and producing metabolites with antimicrobial effects [120].

Lactobacillus and *Bifidobacterium* can improve neurotransmitter activity and release in the context of dementia, acting as preventative measures against this particular disease, particularly by promoting the production of acetylcholine, a metabolite closely associated with neurotransmitters in the central and peripheral nervous systems that affect learning and memory processes [120-122].

Dementia is linked to metabolites produced by the gut microbiota [121]. In their study, 82 participants without dementia and 25 with dementia were included. Fecal samples from both groups of patients were examined. The findings indicate that, compared to controls, patients with dementia had greater concentrations of metabolites, such as phenol, p-cresol, indole, and ammonia. Due to its higher risk, fecal ammonia has been associated with the prevalence of dementia, cognitive impairment, and AD [122].

5.3. Epilepsy

Affecting more than 70 million people worldwide, [123,124] and a frequency of between 0.5% and 1% in children under the age of 16 [125], epilepsy is a common and diverse collection of nervous system diseases. Stroke, physical harm, CNS infections, genetic anomalies, cerebral deformities, and other unidentified causes are only a few factors that might cause epilepsy [126].

The primary symptoms of epilepsy include repeated seizures, aberrant network activity characterized by hyper-synchronized bursts, neuroinflammation, cell death, and neurogenesis [127].

Antiepileptic medications are the first-line therapy for epilepsy. Nevertheless, 25-30% of patients with drug-resistant epilepsy typically experience failure with this type of therapy, and they require other therapies, such as vagus nerve stimulation and brain surgery [128].

Patients with treatment-resistant epilepsy have changed gut microbiota with increased numbers of uncommon bacteria, such as those belonging to the phyla Firmicutes and Verrucomicrobia, and reduced commensal bacteria (zonisamide and lamotrigine are two examples of antiepileptic medications) [123, 126]. Neisseria, Lautropia, Delftia, Campylobacter, and Haemophilus are members of the phylum Proteobacteria and include healthy controls. was more prevalent in 30 patients with idiopathic focal epilepsy [129].

The Fusobacteria phylum was one of several bacterial species in the same study [129] and was only discovered in people with epilepsy rather than in healthy volunteers [130].

Proteobacteria was also found to be more prevalent. The development of epilepsy arises from inflammatory and autoimmune pathways. *Lactobacilli* and *Bifidobacteria*, in conjunction with the restoration of gut microbiota, may provide a preventative factor in the treatment of epilepsy [123]. It has been suggested that a ketogenic diet (KD), a conventional but recently popular treatment for the disease, is a low-carbohydrate, high-fat diet that can treat epilepsy and improve intestinal dysbiosis [131]. According to numerous studies in both humans and animals, the gut microbiota is altered by the use of KD and has a beneficial effect on the symptoms of neurodegenerative, neuropsychiatric, and metabolic disorders [132].

KD's antiepileptic activity of KD has been demonstrated in two animal models [133]. Seizure protection was offered after the microbiota from KD-fed mice were transferred to mice fed a control diet. Despite the gut microbiota in KD-fed mice having less diversity, improvements in *Parabacteroides merdae* and *Akkermansia muciniphila* were observed [133]. They also found that giving the mice simultaneous administration of these two microorganisms had an anti-seizure effect. The outcomes of implementing KD in 20 children with refractory epilepsy were examined in a recent exploratory study after six months [134]. The frequency of seizures in 10 patients decreased by less than 50%, while in the other 10 patients, the frequency increased, or they were seizure-free, and their

electroencephalogram results were also better. It was indicative of the composition of the gut microbiota. Clostridiales, Lachnospiraceae, Ruminococcaceae, Rikenellaceae, and Alistipes are prevalent in patients with poor seizure control [134].

The introduction of probiotic bacteria is another technique for decreasing the severity of seizures, increasing GABA activity, and enhancing cognitive function, as shown in a study on rats administered pentylenetetrazole [135].

5.4. Multiple sclerosis

Another NDs related to inflammation is MS. MS may be caused by changes in the microbiota in the gut and abnormalities in the CNS [136,137]. More than 2.3 million people are affected by MS globally [138,139].

A distinguishing feature of MS is the demyelination of the nervous system cells, which causes neurodegeneration. B cells and autoreactive T lymphocytes, which have affinity for myelin antigens, are immune cells. are responsible for demyelination [138]. In addition to demyelinated lesions, the most common symptoms of MS are fatigue, torpidity, lack of coordination, vertigo, visual loss, muscular pain, bladder and intestinal dysfunction, and depression [140,141].

The microbial flora of the digestive system both promote and control IS and strongly correlate with the severity of MS [142].

The process of demyelination of axons in the brain and spinal cord is influenced by intestinal lymphocytes, cytokines, and chemokines, as well as neurotransmitters (such as GABA, histamine, serotonin, and dopamine) excreted by intestinal microorganisms through the sympathetic or parasympathetic pathways of the CNS [143,144].

Additionally, the production of cytokines and lymphocyte function are disrupted by the formation of aberrant gut microbial metabolites (SCFAs), which could accelerate the inflammatory demyelination process and dementia [145,146].

Pro-inflammatory mediators produced in large quantities (such as TNF), which reduce gut barrier permeability and tight junction protein expression, increase intestinal permeability, microbial translocation, and local and systemic inflammation, are all linked to gut dysbiosis in MS patients [147].

Immunosuppressive drugs that alter the gut microbiota and immunological transcriptome include The following medications are used to treat the symptoms of MS, such as teriflunomide, cyclophosphamide, mitoxantrone, rituximab, daclizumab, basiliximab, methotrexate, mycophenolate mofetil, beta-interferon, and glatiramer (**Figure 6**) [143].

In particular, Butyricimonas species decreased, while *Methanobrevibacter* and *Akkermansia* species increased [148].

Reductions in *Parabacteroides distasonis* and *Prevotella copri* were observed in additional clinical investigations, including individuals with relapsing-remitting MS, while increases in *Dorea* and *Blautia*, the latter two species linked to inflammatory illnesses such as Crohn's disease were observed [149].

Differences in microbial communities such as Bacteroidaceae, Lactobacillaceae, and Clostridiales were observed between MS patients receiving the immunomodulator medication glatiramer-acetate, which is currently used to treat MS, and untreated patients [150]. The same study found that there was an increase in the taxa Coprococcus, Faecalibacterium, and Akkermansia when individuals with MS who had not received glatiramer-acetate treatment were given vitamin D supplements [150].

Given that MS is a complicated condition with numerous linked factors (environmental, genetic, dietary, and lifestyle), improving clinical outcomes for patients with MS may involve modulation of the gut microbiota. The marks left by the gut microbiota may be exploited in their review study of putative biomarkers and pathological signs for the early diagnosis of MS [151].

The intestinal microbiota could also be further investigated for its immunomodulatory characteristics to concurrently treat MS [151].

6. The Microbiota-Gut-Brain Axis and Neuropsychiatric Diseases

6.1. Anxiety

Preclinical research accounts for the majority of the data indicating an association between the microbiome, stomach, brain axis, and anxiety. Research into the effects of probiotic supplementation has shown benefits for several anxiety markers. Probiotics and a placebo had similar effects on lowering anxiety symptoms, there was no noticeable difference between the two according to a meta-analysis of research evaluating the efficacy of probiotics for anxiety behaviors that were conducted in randomized controlled trials [152].

The symptoms of anxiety and stress, as well as general depression 42-item Anxiety Stress Scale scores, were reduced in a 12-week *Lactobacillus plantarum* treatment in a placebo-controlled study of stressed people. Compared with placebo, people who received probiotics had reduced plasma cortisol and pro-inflammatory cytokine levels. Healthy people over the age of 30 who received *L. plantarum* medication performed better in terms of primary attention, emotional cognition, and associated learning when compared to groups with placebos and 30-year-olds as participants. The plasma levels of indoleamine 2,3-dioxygenase, tryptophan 2,3-dioxygenase, dopamine-hydroxylase, and tyrosine-hydroxylase are lowered, and probiotic treatment may alter the serotonin pathway. It has been demonstrated that probiotics increase the plasma concentrations of tryptophan hydroxylase-2 and 5-hydroxytryptamine receptor-6 [153].

6.2. Parkinson's disease

The enteric nervous system and parasympathetic nerves are among the earliest and most often affected systems throughout the evolution of PD. Scheperjans *et al.* compared 72 healthy individuals' stool microbiomes to those of Parkinson's patients to draw comparisons [18], who presented the first concrete proof of a link between the microbiome, gut, brain axis, and PD. They found that postural instability and the relative abundance of Enterobacteriaceae were positively associated, and PD patients had a 77.6% lower Prevotellaceae prevalence than healthy controls and reported having trouble walking [18].

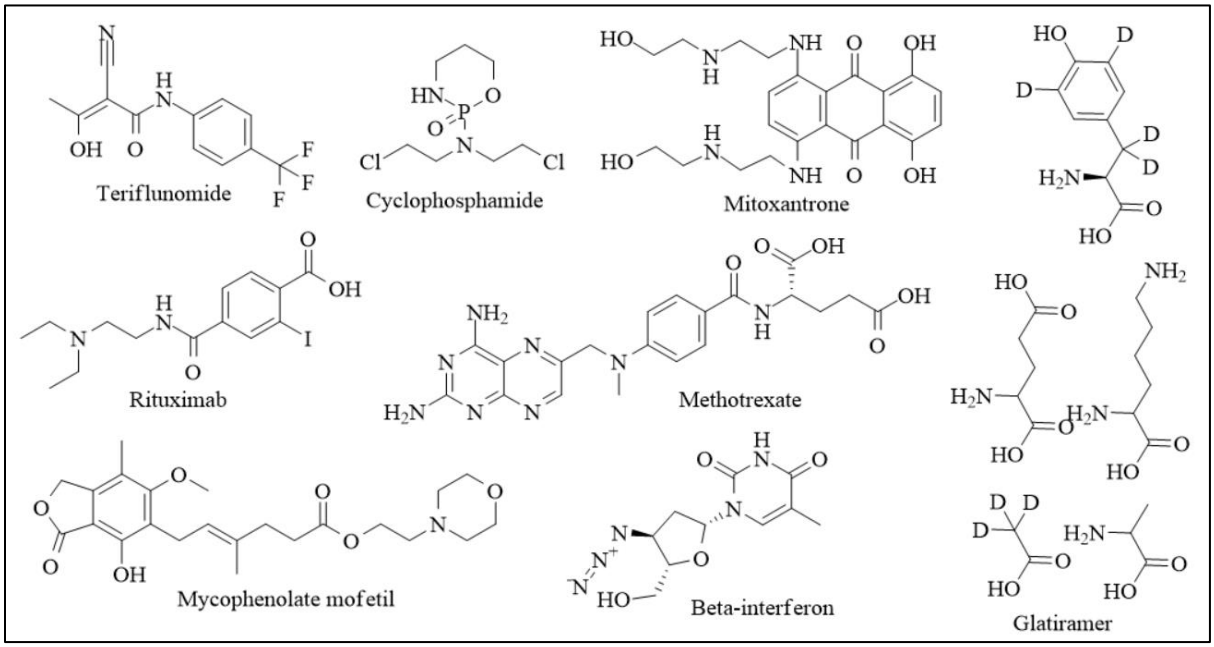

Figure 6. The structures of medications which used to treat the symptoms of MS

In another study, it was discovered that Parkinson's patients had intestinal dysbiosis and lower serum levels of LPS-binding protein. Despite the fact that continuous LPS invasion slightly lowers blood levels of LPS-binding protein, serum levels of LPS-binding protein increase in response to acute LPS concentrations in the blood. Although continuous LPS invasion slightly lowers blood levels of LPS-binding protein, serum levels of LPS-binding protein increase in response to acute LPS concentrations in the blood [154].
The acute LPS concentrations in the bloodstream cause LPS-binding proteins to opsonize LPS more effectively. A clinical experiment involving *Lactobacillus fermentum* was administered to patients with PD, with pre- and post-intervention assessments using the Movement Disorders Society's unified PD rating scale. Probiotic therapy increases enzymatic defense, lowers high-sensitivity C-reactive protein levels, minimizes oxidative damage, and decreases OS [155].

6.3. Major depressive disorder

The pathophysiology of depression has been linked to disturbances in gut-microbiota axis homeostasis. The distribution of prebiotics or placebo to 110 depressed patients was done at random (galactooligosaccharide), in a recent trial, participants received either probiotics (*B. longum* and *L. helveticus*) or a placebo for 8 weeks. Patients with major depressive disorder (MDD) experienced improvements in their Beck Depression Inventory scores during treatment despite the fact that prebiotic supplementation had no impact [156].
The FMT was used in a case study to treat a senior woman with depression. She experienced less fatigue, had a better appetite, and was more social on the fourth day after treatment. She gained weight and was able to live alone after two weeks. After six months, she had lost weight, her constipation problems had subsided, and she received a Patient Health Questionnaire-9 score of 4, down from 21 [157].
The treatment with milk beverage-infused *Lactobacillus casei* resulted in increased mood ratings in a sample of healthy older persons, with the highest benefits shown in those whose mood was initially low [158].
Taking a probiotic supplement that includes *Lactobacillus acidophilus* and *Lactobacillus casei*, and in a clinical study with 40 MDD patients who used a placebo, Bifidobacterium bifidum also lessened depressive symptoms [159].
In a recent open-label trial, it was discovered that taking the probiotic *Clostridium butyricum* along with an antidepressant significantly reduced the symptoms of treatment-resistant depression in patients [160].

7. Potential Therapeutic Uses of Microbiota-Oriented Therapy in Psychiatry

7.1. Prebiotics

The majority of prebiotics are indigestible carbohydrates that aid in the development of good bacteria, or to put it another way, and in the movement of beneficial microorganisms. Prebiotics, such as fructo-, galactic-, xylo-, and inulin-oligosaccharides, are frequently employed [161].
In the colon, they undergo short-chain fatty acid (SCFA) transformation by the bacteria that reside there, which has been shown to have anti-inflammatory effects in IBS [162].
After 12 weeks, *L. rhamnosus* GG, Bifidobacterium lactis, and a particular oligofructose-enriched inulin were combined symbiotically. As a result, the quantity of *Clostridium perfringens* decreased by 31% and the quantity of lactobacilli increased by 16% and 18%, respectively [163].

7.2. Probiotics

Henry Tissier of the Pasteur Institute discovered the first Bifidobacterium (*Bacillus bifidus* communis) in 1899, while studying a breastfed infant. Elie Metchnikoff, a Russian scientist and Nobel Prize winner, proposed that lactic acid bacteria have health advantages that could lengthen their life. By altering the gut microbiota and swapping out proteolytic microorganisms (such as *Clostridium*) with more beneficial microbes, he proposed that "intestinal auto-intoxication" and the ensuing

ageing may be prevented. He formed a diet that included milk fermented with a microbe he dubbed "*Bulgarian bacillus*." The word "probiotics" was originally used in 1965 by Lilly and Stillwell [164].

Nowadays, probiotics (**Table 1**) are widely regarded as live bacteria, preferably of human origin, which, when consumed in a specified and sufficient quantity, provide the host with non-specific health advantages [165].

Increased mucin expression, decreased bacterial overgrowth, and probiotics may maintain the mucosal barrier through increased mucilage immunity (secretory IgA) and the synthesis of antioxidant substances, among other mechanisms [166,167].

In modern commercial formulations, *Lactobacilli*, including the bacterial strains casei, reuteri, fermentum, plantarum, paracasei, salivarius, and rhamnosus, and also the most commonly used probiotics are those of the genus *Bifidobacteria* [168-170].

Probiotics have long been used to treat psychiatric disorders. In fact, despite the fact that Lactobacillus pills and powder were ineffective, Dr. George Porter Philips reported this in 1910. Melancholic adults' melancholy symptoms were alleviated by a gelatin-whey mixture containing live lactic acid bacteria [171].

The usefulness of probiotics in the treatment of a range of ailments (mainly digestive disorders) is currently disputed. The utilization of various species/strains, dosages, treatment durations, and administration methods in different research treatment regimens further complicates this situation. Probiotics can also be consumed as food. The ability to live in the stomach is considered as 35% of the lactic acid bacteria found in fresh fruits and vegetables were found to be present [172].

By increasing the amount of either *Bifidobacterium* or *Lactobacillus* present in the human gut after administration of a single strain, it is possible to infer that the enteric microbiota has undergone even more significant alterations [173,174].

Over the course of two months, daily dosages of *Lactobacillus casei* were administered to 39 CFS patients, which were linked to a significant reduction in anxiety symptoms [175].

Oral probiotic therapy has also been demonstrated to be helpful in reducing SIBO linked to anxiety-depressive diseases [176].

In healthy participants, it was discovered that taking *Lactobacillus helveticus* and *B. longum* twice a day for two weeks reduced anxiety and depressive symptoms [177].

All mental conditions, including depression, anxiety, autism, schizophrenia, bipolar disorder, and alcoholism, have been linked to increased intestinal permeability. Hence, probiotics may be a useful treatment for these conditions. However, orally ingested *L. casei* milk was associated with possibly harmful effects on recall memory, and 132 healthy adults did not notice any change in mood, despite having a high baseline mood [158].

Probiotics are present in a variety of species, and some have been proven to have antiproliferative effects on *Clostridium* species [178-182], leading some authors to advocate probiotic adjuncts in the treatment of autism with varying degrees of success [183].

In the short and medium terms, using probiotics had no negative effects, the Evidence-based Southern California Practice Centre recently evaluated 622 studies, and their findings were as follows: the long-term implications of probiotic use are yet unknown [184].

7.3. Postbiotics

A novel strategy for enhancing microbiota involves initially identifying the chemicals that provide a meal that contains either the depleted molecule or a precursor molecule that can be transformed into a bioactive molecule by the microbial community to restore molecules that are depleted in a certain state. This approach is particularly appealing given that postbiotics are a significant class of functional chemicals used by the microbiota to influence human health [188,189].

Table 1. The primary neurologic of probiotics effect on neurologic disorders in pre-clinical research including adults and children

Study design	Primary neurologic results	Ref.
Four weeks of fermented milk with *B. animalis* subsp. lactis, *S. thermophiles*, *L. bulgaricus*, and *L. lactis* subsp. lactis against placebo were the subjects of a randomized controlled clinical trial.	Decrease in the probiotics arm's reactivity to unpleasant emotional stimuli	[185]
Patients with chronic fatigue syndrome treated with *L. casei* strain Shirota vs placebo for two months were included in a double-blind, placebo-controlled, randomized study.	Reduced symptoms of anxiety in the probiotic group	[175]
Three weeks of treatment with *L. plantarum* WCFS1 or placebo was administered to children with ASD aged three to sixteen in a randomized, double-blind, placebo-controlled research.	Anxiety, disruptive antisocial behavior, and communication issues improve in the probiotic arm	[186]
Randomized study in preterm newborns treated for six weeks with either *L. rhamnosus* ATCC 53103 or *L. reuteri* ATCC 55730, or no supplementation	At one year of age, the control group had a higher rate of poor neurological scores than either of the probiotic groups.	[187]

One class of possible postbiotic substances includes amino acid derivatives that are transformed by gut bacteria. For instance, intestinal epithelial cell expression of pro-inflammatory transcription factors, inflammatory markers, and pathogen colonization are all decreased by the tryptophan-derived compound indole, while mucin production and tight-junction resistance are increased [190].
The correlation between variations in butyrate, acetate, and propionate abundance and health decline in elderly people serves as further evidence of the significance of bacterial SCFA synthesis in GI tract physiology [191].

7.4. Antibiotics and the gut-brain axis

Numerous antibiotics have significant unexpected consequences for local flora. These properties have been therapeutically applied to treat mental disorders. For instance, the second-generation tetracycline minocycline demonstrated therapeutic effects in the treatment of alcoholism, depression, and schizophrenia. Alteration of the gut microbiota among other routes may be the cause of these effects [192,193]. Usually, after the antibiotic course is completed, the local microbiota has an amazing potential to rebound. These therapeutic effects may have been hindered by the recovery. For instance, communication and behavior scores of autistic children improved with vancomycin (**Figure 7**), a medication that effectively fights *Clostridium* bacteria (used to treat *Clostridium difficile* colitis), administered for 8 weeks [32]. However, these scores declined once treatment was stopped. However, the native microbiota does not, considering that certain species-level changes appear to continue for a very long period, usually completely returning to its previous state, this could be helpful in extending therapeutic benefits over the period of antibiotic treatment [194,195].

7.5. Diet modification

A controlled feeding experiment including 10 participants from the same study revealed that while enterotype identity remained consistent over the course of the 10-day experiment, changes in microbiota composition may be noticed within 24 h of beginning a high-fat/low-fiber or low-fat/high-fiber diet [196].
An average Western diet that is heavy in fat and poor in fiber will increase plasma endotoxin activity by 71% after one month. In comparison, in healthy individuals, a 6-week very low energy diet specifically had an effect on *bidifidobacteria*, and switching for a month to a low-saturated fat, high-fiber diet can reduce baseline blood endotoxin activity by 38%, which is not based on the average weight of 16 obese persons [197].

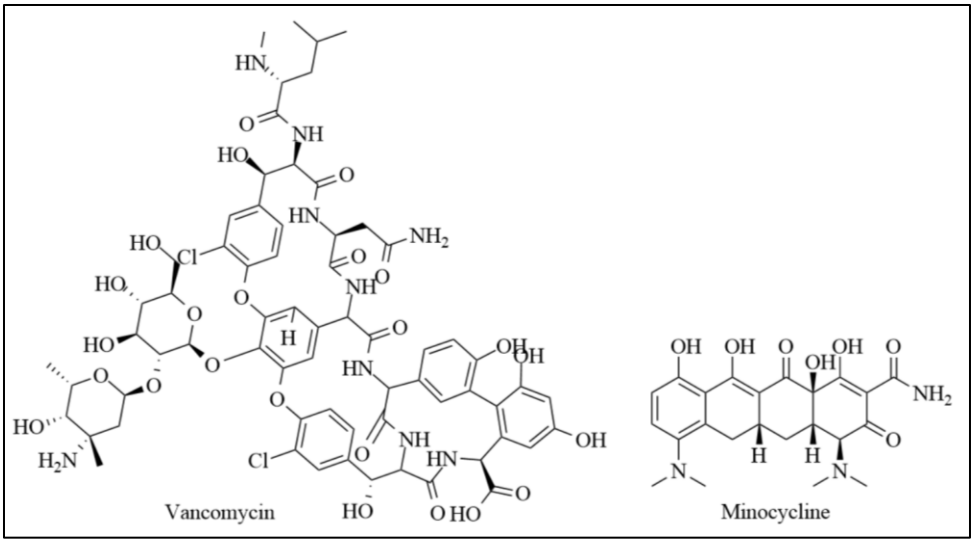

Figure 7. The structures of minocycline and Vancomycin

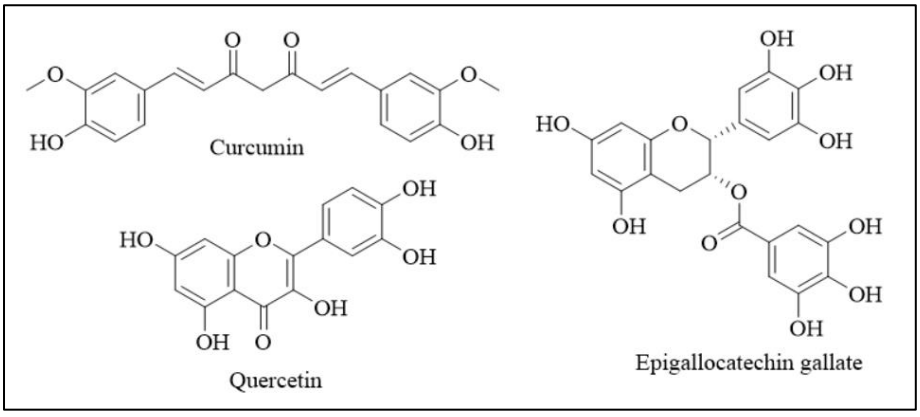

Figure 8. Polyphenolic dietary compounds—curcumin, EGCG, and quercetin—and their neuroprotective potential

Firmicutes species in three different cohorts of obese European adults provided baseline predictions of the responsiveness of microbiota to dietary changes [198].

The composition of microbial communities is altered by the short-term use of diets that contain only animal or plant sources and eliminate inter-individual differences in the expression of microbial genes. The number of bile-tolerant bacteria (Alistipes, Bilophila, and Bacteroides) increases in response to an animal product-rich diet [199].

More than 500 cultured isolates' genomes were sequenced using a low-error 16S ribosomal RNA amplicon sequencing technique, 37 American subjects who had been observed for up to 5 years, were able to provide a description of the bacterial strain makeup in their gut microbiota [200].

However, shared strains were not found in random individuals; only family members were tested. Changes in weight were a stronger predictor of changes in strain composition than variations in sampling intervals after taking up to 32 weeks of a boring liquid diet. One day, the gut microbiota serves as a diagnostic tool, and due to its stability and sensitivity to physiological changes, it has become a good therapeutic target. Various prominent antioxidant-rich foods, including chocolate, In epidemiological research, it has been discovered that coffee, green tea, blueberries, and curcumin all promote the growth of *Lactobacilli* and *Bifidobacteria* [201,202].

Coffee use has been linked to an increased risk of developing depression and/or cognitive decline [203].
Curcumin prevented the permeability of the BBB caused by LPS in an experimental model, while green tea reduced it and "Sickness behavior" is the term used to describe a coordinated set of adaptive behavioral changes that occur in sick persons over the course of an disease [204].
Orange juice, as opposed to plain or sweetened water, is more beneficial when drunk with a high-fat/high-carbohydrate (low-fiber) diet that decreases the levels of circulating endotoxin, perhaps as a result of its high flavonoid content [205].
Animal studies have demonstrated that the long-term use of honey, a staple of traditional feeding practices, can counteract the effects of LPS and is linked to the growth of *Lactobacilli* and *Bifidobacterium* [206].
Additionally, compared to controls who followed a sugar-free and sucrose-free diet, there was a decrease in anxiety and cognitive loss [207].
Depressive symptoms, quantification of alterations to cecal *Bifidobacteria* and *Lactobacilli in vitro*, and low magnesium levels have all been linked [208].
Zinc has an impact on intestinal permeability as well as the diversity of gut bacteria, and when taken insufficiently over the long term, a different vitamin has consistently been linked to depression [209]. Intestinal alkaline phosphatase, a crucial enzyme involved in maintaining the variety of gut microbiota and reducing the load of systemic LPS, requires these two chemicals to function properly [209].
Dietary polyphenols such as curcumin, epigallocatechin gallate (EGCG), and quercetin (**Figure 8**) modulate gut microbiota and neuroinflammation. Their polyphenolic structures interact with microbial enzymes and ROS.

7.6. Fecal transplantation

The most drastic alteration in the gut flora can be considered fecal transplantation. With fecal transplantation, unhealthy gut microbiota is replaced or replenished using the microbiota of a healthy donor. Faecal transplantation is effective in treating refractory *C. difficile* infection with a 90% success rate [210,211].
The inherent risk of exposing the recipient to new harmful microorganisms prevents fecal transplantation from being routinely used. However, this strategy might be utilized more frequently in the future if further studies into the action mechanisms, implications on the host's immune system, and the development of the microbial inoculum are still ongoing [212].

8. Limitations and Future Challenges

Despite promising evidence linking gut microbiota to neuropsychiatric and neurodegenerative diseases, several limitations hinder translational progress. One major challenge is inter-individual variability of the gut microbiome, which can lead to inconsistent responses to probiotic or dietary interventions. Factors such as genetics, diet, geography, age, and antibiotic use contribute to microbiome diversity, thereby complicating the generalization of therapeutic effects. Furthermore, many findings are based on animal studies, and translating these results to human clinical contexts remains difficult because of physiological and metabolic differences. Human trials are often limited by small sample sizes, a lack of longitudinal data, and ethical constraints, making it challenging to establish causal relationships. Another significant limitation is the bioavailability and stability of microbial metabolites, such as SCFAs and tryptophan derivatives, which can degrade rapidly or may not effectively cross the blood–brain barrier. Analytical challenges persist in identifying and quantifying these metabolites in complex biological matrices. Standardization of methodologies, more robust clinical trials, and personalized approaches are essential to overcome these barriers and harness the full therapeutic potential of the gut–brain axis.

9. Conclusion

This review elucidates the intricate chemical and microbial interactions underlying gut–brain communication and their implications in neuropsychiatric and neurodegenerative

disorders. Key findings demonstrate that microbial metabolites, such as γ-aminobutyric acid (GABA), short-chain fatty acids (SCFAs), tryptophan derivatives (*e.g.,* indole and kynurenic acid), and LPS modulate neuroinflammation, neurotransmission, and blood–brain barrier integrity. These compounds interact with host receptors through well-characterized structural features such as aromaticity, polarity, and carboxylic functional groups, making them prime candidates for therapeutic targeting. Specific therapeutic opportunities include the modulation of microbial communities using prebiotics, probiotics, postbiotics, dietary polyphenols, and fecal microbiota transplantation to restore the neurochemical balance. Pharmacological agents such as minocycline, vancomycin, and metformin also show promise by altering microbial populations and reducing inflammation. Notably, SCFA-producing bacteria, Lactobacillus rhamnosus, Bifidobacterium, and Akkermansia muciniphila, have demonstrated neuroprotective effects in conditions such as Alzheimer's, Parkinson's, autism, epilepsy, and major depressive disorder. The chemical pathways meriting further investigation include the kynurenine pathway, serotonin synthesis from tryptophan, GABAergic signaling, and the indoleamine 2,3-dioxygenase axis. Additionally, postbiotic interventions that replenish depleted microbial metabolites and block proinflammatory cascades are promising therapeutic frontiers. Future research should emphasize structure–activity relationships and targeted modulation of microbial metabolism for precision therapies in neuropsychiatric and neurodegenerative diseases. Precision targeting based on microbial profiles can enable patient-specific interventions such as selecting probiotic strains that boost SCFA production in individuals with Parkinson's disease or inhibiting specific indole-producing bacteria in patients with autism spectrum disorder. Personalized microbial therapies can be modeled using machine-learning algorithms trained on microbiome sequencing data, metabolomic outputs, and clinical phenotypes to predict the most effective microbial modulators for each patient. Progress in the understanding of pathogenic microorganisms and the role of microbiota in chronic neurologic and psychiatric disorders is significant, but further study is needed to develop effective therapeutic strategies.

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Conflicts of Interest

There is no conflict of interest exists.

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