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Review

The Biomolecular Basis of Gut Microbiome on Neurological Diseases

Roberto Anaya-Prado [1, 4, *], Ana P. Cárdenas-Fregoso [1, 4], Ana M. Reyes-Perez [1, 4], Danielle M. Ortiz-Hernandez [1, 4], Montserrat Quijano-Ortiz [1, 4], Monica V. Delgado-Martinez [1, 4], Ana S. Pelayo-Romo [1, 4], Roberto Anaya-Fernández [1, 2], Michelle M. Anaya-Fernández [1, 3], Consuelo C. Azcona-Ramírez [1, 3], Ivan F. Garcia-Ramirez [1, 3], Miguel A. Guerrero-Palomera [1, 3], Daniel Gonzalez-Martinez [1, 3], Citlalli S. Guerrero-Palomera [1, 3], Karina Paredes-Paredes [1, 3], Claudia Garcia-Perez [1, 3]

1. Division of Research & Education at Centro Médico Puerta de Hierro, Guadalajara, Jalisco, Mexico; E-Mails: robana1112@gmail.com; roberto.anaya@tec.mx; anapaulacaf@outlook.com; anarperez8@gmail.com; lnbmichelle.ortiz@gmail.com; montserratqonutri@gmail.com; monicadelmaa@gmail.com; sofiapelayor@gmail.com; anayafernandezroberto@gmail.com; michanafer@gmail.com; consuazcona@gmail.com; ivan.fabritzio@gmail.com; gromiguel@hotmail.com; daniel.gmartinez@hotmail.com; lali.g.p@outlook.com; karinaparedes9809@gmail.com; claugap23@gmail.com
2. School of Medicine at Centro Universitario de Ciencias de la Salud, University of Guadalajara, Guadalajara, Mexico
3. Autonomous University of Guadalajara, Zapopan, Mexico
4. School of Medicine and Health Sciences, Tecnológico de Monterrey, Guadalajara, Jalisco, México

* **Correspondence:** Roberto Anaya-Prado; E-Mails: robana1112@gmail.com; roberto.anaya@tec.mx

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Special Issue: Gut Feelings: The Role of the Human Gut Microbiome in Neurological Health and Ill Health

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Abstract

The human gastrointestinal (GI) tract harbors many microorganisms, including viruses, protozoa, archaea, fungi, and bacteria. Altogether, these microbes constitute what we know

as the gut microbiome (GM). These commensal communities have important implications for human health. They influence physiological processes through different mechanisms, including synthesizing neurotransmitters, regulating enzymatic pathways, and releasing molecules responsible for different signal pathways. The interaction between GM and brain function has been associated with the development and pathogenesis of neuropsychiatric diseases. This review discusses current studies targeting the regulation and modulation of GM in nerve, neuroendocrine, and immune pathways. Thus, we analyze current evidence on transcription, changes in composition, and specific interactions between the gut and brain from a biomolecular perspective. Special attention is paid to mood disorders and neurodegenerative diseases.

Keywords
Neurodegenerative diseases; microbiota; gut brain axis; neurotransmitters; central nervous system; neurological diseases; psychiatric diseases; molecular pathways; dysbiosis

1. Introduction

The human gastrointestinal tract harbors many microorganisms, including viruses, protozoa, archaea, fungi, and predominantly bacteria. Altogether, these microbes integrate what we know as Gut Microbiome (GM). GM is estimated to encompass 10^{14} microorganisms of many species, including Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria [1, 2]. Yet, Firmicutes and Bacteroidetes are the main species in the gut [2, 3]. Colonization of microbial communities begins early in childbirth and upon delivery: either by cesarean section or vaginal delivery. Maternal gestational diet and weight gain, breastfeeding or artificial formula, gestational age, and birthplace all contribute to gut microbiota in the newborn [2]. Diversity and number of bacteria increase while growing up as environmental elements in the gut. Both host-extrinsic and intrinsic factors modify their taxonomic composition [4]. These changes influence immunity, endocrine, metabolic, and neurologic performance [5]. Therefore, every human body holds an individual microbiome. Despite the uniqueness of GM, there are now compelling data with particular species 'signatures' associated with certain conditions. The influence of many elements makes up the final composition: exposure to bacteria in childhood, age, genetics, infections, environmental factors such as nutrition, physical activity, stress, sleep, and the use of antibiotics [6].

Gut Microbiome has vital effects on human health, as it maintains homeostasis, regulates both the central nervous system (CNS) and enteric nervous system (ENS), impacts immunomodulation, and has a bidirectional relationship with the host organism (physiology) [7, 8]. Therefore, it participates in physiological and biochemical processes through different mechanisms. These include, but are not limited to, the synthesis of neurotransmitters, metabolites and immunomodulators, nutrient absorption and metabolism, enzyme regulation pathways, and release of molecules responsible for various signal pathways (Figure 1) [9, 10].

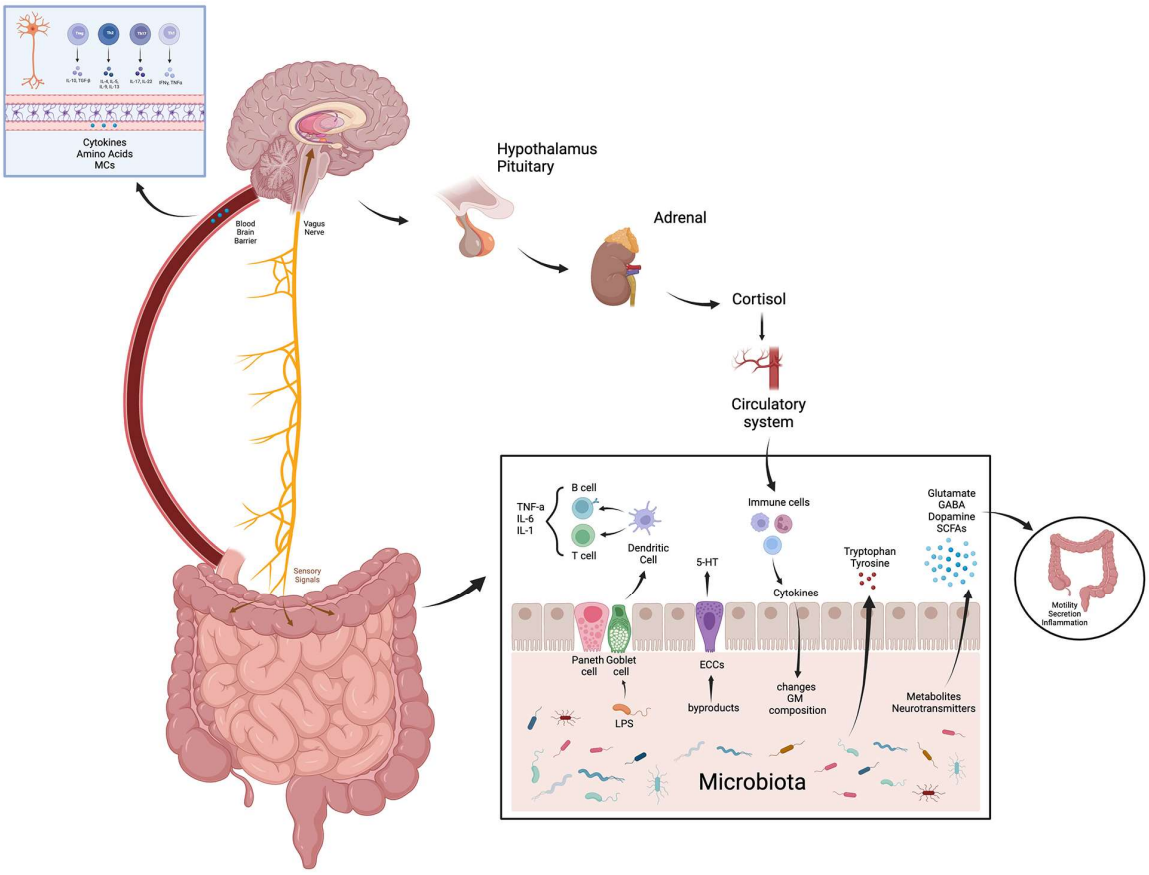

Figure 1 In this figure, different pathways of communication between gut microbiota (GM) and the brain are outlined. Gut-brain axis (GBA) plays a key role in this molecular connection. This bidirectional interplay involves microbial metabolite signaling, cytokines, the vagus nerve, and the hypothalamic-pituitary-adrenal axis. Synthesized neurotransmitters in the gastrointestinal tract (e.g. GABA, Dopamine) by GM may lead to altered bowel motility, secretion, and inflammation. SCFAs, short-chain fatty acids; GABA, gamma-aminobutyrc acid; LPS, lipopolysacharide acid; TPH, tryptophan hydroxylase; 5-HT, 5-hydrositriptamine (serotonin); ECCs, enterochromaffin cells; TNF, tumor necrosis factor; IL, interleukins; Th, T helper; IFN-γ, interferon Gamma; Treg, regulatory T cells; TGF-α, transforming growth factor; BBB, blood-brain barrier. MC, mast cells.

2. Objectives

This review discusses current studies targeting regulation and modulation of gut microbiome in nerve, neuroendocrine and immune pathways. The purpose is to analyze up-to-date evidence on signaling, changes in composition (conformation), and specific interactions between the gut and brain from a biomolecular perspective. Special attention is paid to the mechanisms involved in the pathogenesis of mood and neurodegenerative disorders. Depression, Bipolar disorder (BD), Anxiety, Parkinson's disease (PD), Alzheimer´s disease (AD), and Multiple Sclerosis (MS) are some of the pathologies reviewed. Interaction mechanisms between the gut and brain and how specific bacteria alter brain work are also reviewed.

3. Neurological Diseases

Neurodegenerative diseases (ND) are a group of disorders characterized by a progressive loss of structure or function of neurons, which are the specialized cells that carry information in the nervous system. Various conditions, including genetic mutations, environmental toxins, and aging cause these diseases. Some of the most common ND include AD, PD, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS). Memory loss, motor problems, difficulty speaking, and changes in mood or behavior are some of the symptoms caused by these syndromic conditions. No known cure for most neurodegenerative disorders has yet been described, and treatment has been focused on managing symptoms and improving life quality. Research in this field is in progress, and new therapies are being developed. Hopefully, new treatments will slow down disease progression, thus improving patient outcomes [11].

Mood disorders have also been described as a group of mental health conditions that affect a person's emotional state and overall well-being. They are characterized by significant changes in mood, energy level, and behavior that can impact a person's daily life and ability to work [12]. Genetics, brain chemistry, life experiences, and environmental factors are the main leading causes of mood disorders [13]. Management usually involves a combination of therapy, drugs, and changes in lifestyle. With proper treatment and support, most patients can manage their symptoms and lead a fulfilling life [14].

3.1 Relationship Between Gut and Psychiatric Disorders

Recent findings suggest that GM regulates brain activity and cognitive abilities. Microbes facilitate the interaction between the CNS and the immune and metabolic processes through the microbiota-gut-brain axis (Figure 1) [15]. The communication between these two biological systems occurs through different mechanisms, such as signaling through epithelial receptors, modulation of the immune system, and stimulation of enteric neurons by bacterial metabolites. It has been demonstrated that GM regulates the amount of circulating tryptophan, which induces serotonin (5-HT) synthesis. It can also modify the expression of specific receptors in the CNS, directly affecting brain function and excitability. Neurotransmitter imbalances may lead to neurological and psychological disorders like AD, PD, autism spectrum disorder, anxiety, and depressive conditions. Investigating dysregulation of neurotransmitter production in both the CNS and peripheral organs could provide knowledge of these conditions' molecular origins. Additionally, microbiota can use epigenetic control over gene expression [16].

Therefore, the connection between GM and the brain has been investigated for many years. However, a definitive conclusion has yet to be reached. Different methodologies utilized by researchers may explain inconclusive results. Inclusion criteria are not uniform, so analysis cannot be performed accordingly. Patient characteristics, such as age, diet, physical activity, morbidities, disease stage, and medical condition, have not been stratified in every study. Therefore, results cannot be extrapolated to the general population.

4. Gut-brain Axis: Neuropsychiatric Diseases

Evidence suggests that there is bidirectional communication between the GM, key components of the CNS, and immunologic pathways. These involve both direct and indirect message pathways.

The autonomic nervous system (vagus nerve), the immune system (inflammatory biomarkers), the endocrine Hypothalamic-Pituitary-Adrenal axis (HPA), and the enteric nervous system (ENS) play vital roles in these pathways [6]. The vagus nerve connects the gastrointestinal tract to emotion-regulating regions in the brain, including the *nucleus tractus solitarius*. This nerve contains vagal fibers that can recognize molecules supplied by GM; such as neurotransmitters (5-HT, dopamine, γ-aminobutyric acid), bacterial metabolites, and short-chain fatty acids (SCFAs). These molecules can actively modulate gastrointestinal performance: secretion, motility, and inflammation, and they can even control the host's mood (Figure 1) [17, 18].

The vagus nerve also has a close connection to the ENS. It serves as a communication route between the CNS and the sensory signals transferred by specialized structures of endocrine and enterochromaffin cells [10, 17]. Enterochromaffin cells (ECCs) in the gut epithelium contain more than 90% of the body's 5-HT, whose synthesis is modulated by SCFAs produced by gut microbes, particularly *Bifidobacterium infantis*. This microbe reacts when there is an increase in tryptophan consumption [17, 19, 20]. The ENS can directly modulate the microbial composition of GM through changes in permeability, immunological responses, and motility. An autonomic nervous system-mediating control can indirectly modulate gut physiology, and the central nervous system controls this autonomic system [17, 19].

4.1 Neurotransmitters, Metabolites and Gut Microbiome

A specific taxonomic group of bacteria is responsible for encoding genes for enzymes to catalyze the conversion of substrates into neurotransmitters or their precursors. Many of these compounds are amino acids, like tryptophan and tyrosine, which develop from the diet. Then, they enter the bloodstream, follow up to the blood-brain barrier (BBB), and are enzymatically transformed into neurotransmitters. Dopamine, SCFAs, 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), and glutamate are some of the metabolites produced by human GM [15]. These can modulate interactions associated with immunity and neurophysiology in the host. However, specific information on human brain structures and functions remains unknown [20].

4.2 Bidirectional Communication of the Gut-brain Axis: How it Works

Microorganisms residing in the gut can trigger host's innate immune response. This can further stimulate inflammasomes and several immune cells, including T-cells, B-cells, and T-helper (Th) cells. Inflammasomes and immune cells are instrumental in either pro or anti-inflammatory responses [18]. Lipopolysaccharides and endotoxins produced by bacteria can also stimulate the immune response. Immune cell infiltration into the brain is then promoted, thus triggering CNS inflammation. These hyperactive mechanisms of the immune system may trigger a counterregulatory reaction that involves the HPA axis. This axis is responsible for producing glucocorticoids, key elements of the stress response to injury. It is also responsible for the adaptive capacity to environmental stimuli, which is critical for every human being. Nonetheless, a sustained inflammatory stimulus may lead to a dysfunctional HPA axis, eventually increasing the risk for mental health disorders [18]. Therefore, GM synthesizes neurotransmitters and their precursors in the intestinal lumen. Subsequently, they may cross the BBB, impacting the CNS role. The gut-brain axis (GBA) plays a key role in this molecular connection studied in animal models [6]. Therefore, changes in GM can affect the synthesis of neurotransmitters and their precursors. Accordingly, the human microbiome has

been associated with a broad range of neurological disorders, such as MS, PD, AD, Depression, Anxiety, and BD, among others [15].

4.3 Gut Dysbiosis

Gut dysbiosis (GD) occurs when microbiota conformation becomes abnormally altered. Accordingly, there is an imbalance between intestine pathogenic microorganisms and microbial antigens. An increase of Firmicutes and Bacteroidetes has been described as a vital characteristic of these disparities [21]. Others have observed a reduction of Bifidobacteria [20]. GM shows a large heterogeneity (bacteria, archaea, fungi, and viruses), which helps maintain intestinal homeostasis. However, diet, antibiotics, lifestyle, diseases, and genetics have all been observed to affect the regular balance of GM [21]. This explains why irregular changes in GM have been reported to be involved in the pathophysiology of many neurological disorders, such as AD, MS, PD, and schizophrenia (SCZ) [20-22]. In addition to the changes in the intestine "environment", an altered communication across the gut-brain axis has been reported [20]. Dysbiosis influences inflammation and CNS activity by altering vagal and/or spinal nerve routes. In stress-related conditions, the interplay between microbiota and the immune system is substantiated by findings indicating that recurring stress exposure affects GM with shifts in pro-inflammatory cytokine levels [6, 20].

5. Pathogenesis in Mood Disorders

5.1 Depression

Depression is a complex disorder that involves alterations in different biomolecular pathways in the brain. These include, but are not limited to, the inflammatory, oxidative stress, neuroplasticity, neuroendocrine, and the neurotransmitter system [23]. Levels of certain neurotransmitters, such as 5-HT, norepinephrine, and dopamine, are altered in depression. These neurotransmitters are involved in regulating mood, motivation, and pleasure. Furthermore, the HPA axis, which is a significant stress response system in the body, is dysregulated in depression. This leads to increased levels of the stress hormone cortisol, which is associated with negative mood and cognitive impairments. Depression is also associated with increased inflammatory biomarkers, such as cytokines. In humans, these biomarkers can cross the BBB and trigger immune cells in the brain, leading to neuronal damage and dysfunction [24].

Oxidative stress (OS) represents an imbalance between the production of reactive oxygen species (free radicals) and the ability of the body to detoxify them. It is believed that OS contributes to the development of depression as it can damage specific cellular components, including DNA and proteins. Therefore, OS impairs neuronal function [25]. Neuroplasticity represents the ability of the brain to adapt and change in response to experience. However, it is believed that this capacity is impaired under depression conditions. This impairment can lead to decreased neuronal connectivity and function, which may contribute to the symptoms of depression [26]. Unaffected neuroplasticity allows the brain to identify synaptic connections and work without a problem when learning (mental work) or even following injury [26]. Overall, depression is a complex disorder that involves alterations in multiple biomolecular pathways in the brain and body. Understanding these pathways may help identify new targets for developing novel antidepressant treatments [27, 28].

5.2 Bipolar Disorder

Bipolar Disorder (BD) is a chronic or episodic neuropsychiatric mood disorder characterized by episodes of fluctuation between mania and depression with an euthymic state [8, 29-32]. Pathogenesis is known to be multifactorial. Genetics, environmental interaction, imbalances in monoaminergic neurons, changes in neuroplasticity, dysregulation of mitochondrial function, neuroinflammatory processes, autoimmunity, stress axis activity, oxidative stress, and chronobiology have all been described as leading causes of BD [8, 29, 30]. Since GM plays a vital role in the modulation of immune response, it could also modulate BD [8]. From a biomolecular perspective, patients with BD have shown increased pro-inflammatory biomarkers such as NF-kB, IL-6, IL-1B, IL-2, IL-4, and TNF-a (Figure 2). These cytokines have been shown to decrease levels of 5-HT and brain-derived neurotrophic factor (BDNF) [29, 30]. Moreover, gram-negative bacteria produce lipopolysaccharides (LPS). These endotoxins enter the bloodstream by intestinal absorption. Thus, Toll-like receptor-4 (TLR4), located on the surface of enterocytes, recognizes and binds with LPS, subsequently triggering the production of proinflammatory cytokines (IL-1a, IL-1b, TNF-a, IL-6). All these are capable of active-stimulating the CNS due to the permeability of the BBB [8, 33].

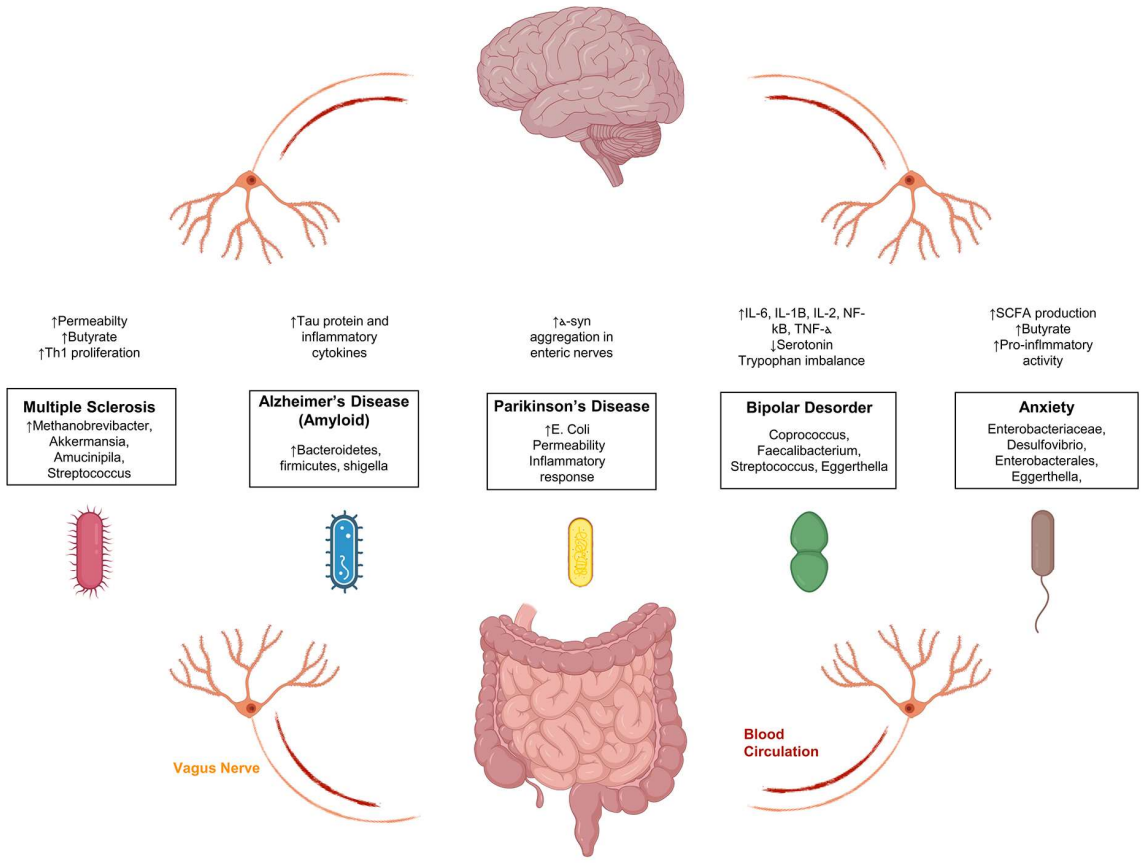

Figure 2 Gut Microbiota involved in Neurological diseases through different biomolecular pathways. TNF-α, Tumor Necrosis Factor - alpha; IL, interleukins; Th, T helper; SCFAs, short-chain fatty acids; a-syn, α-syn, α-synuclein; NF-κB, Nuclear factor kappa B.

Some studies have documented a reduced monooxygenase (KMO) expression in platelets of patients with BD. This enzyme is required for the metabolism of tryptophan into kynurenine (Kyn) through the Kyn pathway, and current evidence suggests that an imbalance in tryptophan and Kyn metabolism may be implicated in the neurobiology of BD [34-36]. The amino acid tryptophan is a precursor of 5-HT. Tryptophan depletion has been demonstrated to interfere with Kyn pathway and 5-HT synthesis [15, 35]. Additional information suggests that imbalances in the serotonergic system are also involved in the pathophysiology of BD [29]. However, dietary intake of tryptophan can further be metabolized through the GM. Specific bacteria can break down this amino acid into indole-3-propionic acid so it can subsequently cross the BBB [5]. Furthermore, 5-HT synthesis can be modulated using GM. This synthesis can be regulated by specific pathogens, such as *Clostridium perfringens,* and by SCFA produced after GM. Tryptophan hydroxylase 1 (TPH1) plays a key role in this synthetic modulation [2, 17]. A systematic review of observational studies and a meta-analysis on BD and Schizophrenia (SCZ) conclude that GM composition in patients with BD, shows a reduction in gram-positive bacteria *Coprococcus, Faecalibacterium, Ruminococcus* and increased levels of *Enterococcus*, *Flavonifractor*, *Streptococcus* and *Eggerthella*. Therefore, they all have been implicated in inflammatory conditions [37-39]. That is, decreased numbers in gram-positive bacteria and increased levels of *Enterococcus*, *Flavonifractor*, *Streptococcus* and *Eggerthella* have been associated with anti-inflamatory and pro-inflammatory conditions, respectively.

5.3 Anxiety

Multiple human studies have reported that Gut dysbiosis, inflammation, and stress are significant contributors to the pathogenesis of anxiety and depression disorders [40]. This inflammatory state is further affected by alterations in GM composition, immune system, ENS, CNS, and the HPA axis, among others. They all eventually lead to neuroinflammation and changes in the synthesis of neurotransmitters [41].

Large amounts of *Enterobacteriaceae, Desulfovibrio, Enterobacterales, and Eggerthella* have all been reported to prevail among clinical cases of anxiety suffering from gastrointestinal inflammation [42]. Lower colonization of five specific genera, including *Butyricicoccus, Sutterella, Eubacterium rectale, Faecalibacterium, and Lachnospira,* has also been associated with gut inflammatory conditions and anxiety [43]. These bacterial genera are major contributors to SCFA compound production, which are key elements in maintaining intestinal integrity [44]. Therefore, lower butyrate concentrations may reduce mucosal barrier integrity, facilitating bacterial translocation [42]. On the other hand, a higher production of endotoxins (lipopolysaccharides) has been associated with the growth of some bacteria. These molecules and an integrated immune response develop changes in intestinal permeability. The pathophysiologic process occurs by increasing sodium-water availability, facilitating endotoxin mobility into the circulation. Subsequently, an actual immune response called “endotoxemia” is initiated [45].

Changes to all: GM composition, its byproducts, intestinal structure, and the production of different endotoxins, altogether trigger an immune response. This reaction involves higher levels of proinflammatory cytokines and acute phase proteins that may lead to immune dysregulation. This reaction has been observed in mental health disorders. Therefore, clinical practice must consider that additional proinflammatory cytokine production is triggered by psychological stress [42]. Murine models show that these cytokines and other inflammatory stimuli travel from the ENS

through vagal afferent fibers and access the BBB. Subsequently, they start-up immune cells in the CNS (microglia); which trigger innate resistance receptors, leading to inflammation in the CNS (neuroinflammation) [41, 42]. Moreover, these immune responses may trigger a stress reaction through the HPA axis in order to balance the proinflammatory activity. Nonetheless, a chronic stress response may lead to dysregulation in the HPA axis. Accordingly, an abnormal and sustained high level of cortisol develops. All this is a common characteristic of anxiety disorders [42]. Therefore, monoamine synthesis (5-HT, dopamine and norepinephrine) is delayed after the modification of tetrahydrobiopterin. During neuroinflammation, proinflammatory cytokines damage this essential enzymatic cofactor [46].

Intestinal integrity, microbial diversity, inflammation, stress response, and mental health have proven to improve with probiotic and prebiotic supplementation [41] promisingly. However, further research is needed to define the strains that benefit the most from these therapies. Furthermore, high-soluble fiber diets that promote SCFA production have decreased proinflammatory cytokine activity and anxiety symptoms [42].

6. Pathogenesis in Neurodegenerative Diseases

6.1 Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative pathology that affects the CNS and progressively leads to motor deficits. It is characterized by the accumulation of alpha-synuclein protein (a-syn), also known as Lewy bodies (LB), and cell death in the brain's basal ganglia. By the end of life, 70% of the dopamine-secreting neurons in the *substantia nigra pars compacta* are affected. This is the cause of movement disorders in patients with PD. They may also show other non-motor symptoms like sleep deficits, rapid eye movement, cognitive impairment, hypersomnia and orthostatic hypotension. Interestingly enough, up to 80% of them suffer from GI symptoms, with "*constipation"* the most common [18].

The presence of LB and neurites in the gastric myenteric and submucosal plexus suggests that damage to the ENS plexus may occur either on early stages of PD or before any symptom appears. Furthermore, innervations of the GI tract may become affected in different stages of PD. Inclusions of α-syn in the olfactory bulb and the dorsal motor nucleus of the vagus nerve (DMV) may occur early in PD, along with other symptoms such as constipation, insomnia, and smell impairment. Later (third stage), the *substantia nigra* may showα-syn inclusions, which may be the cause of movement disorders. This α-syn protein is mainly expressed in presynaptic terminals in the CNS. Accordingly, this protein forms Lewy bodies in cell somata and Lewy neurites in axons and dendrites. These structures have a role in the supply and release of dopamine to modulate neurotransmission. Accumulation of α-syn protein in the ENS damages enteric neurons and has been associated with GI tract dysfunction. Specific anatomical effects have been demonstrated on myenteric and submucosal plexuses in patients with PD. Moreover, α-syn protein excess may spread via the vagal nerve from the ENS to the brainstem, midbrain, basal forebrain, and cortical areas [22].

Current evidence indicates that alterations in GM lead to mucosal inflammation and oxidative stress. This results in α-syn aggregation in enteric nerves and spreads via the vagus nerve into the brain. This phenomenon has been demonstrated in patients with PD [22]. Clinical presentation includes an increased intestinal permeability, tissue inflammation and accumulation of α-syn in the ENS. Some microorganisms, such as *Escherichia coli* lead to high exposure to endotoxins,

inflammation and production of pro-inflammatory cytokines (TNF-α, IFN gamma, IL-6 and IL-1β) [22]. Therefore, in human studies GM has been associated with gut permeability and inflammatory responses in both the gastrointestinal tract and the CNS in PD.

6.2 Alzheimer's Disease

Alzheimer's Disease (AD) involves chronic and progressive degeneration of brain cells, which leads to memory impairment as well as a progressive cognitive decline. In the year 2020, AD affected 45 million people all over the world, along with other forms of dementia. These patients' learning, memory, and behaviour are seriously affected [20, 47]. Alzheimer's Disease has been extensively studied. However, basic etiopathology remains [20]. Neuronal cell death is a common presentation in AD. Synaptic failure with amyloid-β deposits on neurons and phosphorylation of the microtubule-associated protein *tau* are also regular features. These changes contribute to neuron destabilization and lack of homeostasis, which lead to neuronal apoptosis [20]. Over the past decade, there has been a growing interest in the possible role of GM in AD. Thus, some studies suggest that microbes are a likely source for this disease. Moreover, research performed in rats has shown that bacteria can produce amyloid-like proteins and increase α-syn pathology [2].

Animal studies have demonstrated that GM and dysbiosis contribute to the progression of AD. Also, stool tests of patients with AD have documented interesting results. On one side fewer numbers of *Firmicutes* and *Bifidobacterium*, while increased numbers of *Bacteroidetes* on the other, have been associated to AD [47]. Other studies have shown significant amounts of pro-inflammatory Escherichia and Shigella and a reduced growth of the anti-inflammatory *Escherichia rectale*. Both conditions have been associated to a peripheral inflammatory state [2]. Studies have tried to describe the pathophysiology of dysbiosis leading to AD. Colonization of LPS and *Escherichia Coli* with amyloid plaques suggests that gut dysbiosis triggers amyloid pathogenesis. The consequence is systemic inflammation and BBB impairments. Moreover, gut permeability allows LPS translocation from gram harmful bacteria. All these lead to neuro-inflammation that has been associated with AD. Nonetheless, further research is necessary to demonstrate this association [47].

Downstream triggering of cytotoxic and inflammatory mediators has been associated to a higher expression of gut microbial inflammasome proteins. And the "cytoplasmic multiprotein complex NLRP3" plays a key role in the innate immune system and inflammatory signaling. Once NLRP3 inflammasome is activated by PAMPs and DAMPs, caspase-1 is released. This initiates the process of pro-inflammatory cytokines (IL-1β and IL-18) activation. Chronic inflammation is associated with abnormal activation of NLRP3. That is the case of diseases of the CNS, such as: Parkinson's disease (PD), Multiple Sclerosis (MS) and Alzheimer's disease (AD) [48]. Therefore, targeting GM modulation has become a possible treatment strategy for AD. However, more research is necessary to understand this interesting inflammatory pathway further.

Gut microbiota may be altered by diet, which favors access to more microorganisms in the GI tract. These changes trigger the local immune system, promoting an increased epithelium permeability. Endotoxemia develops, which leads to the immune activation of the brain. This low-grade activation is implicated in the pathophysiology of Alzheimer's Disease [49]. Nonetheless, further research is needed to know precisely how dysbiosis affects the mechanisms leading to AD progression.

6.3 Multiple Sclerosis

Multiple Sclerosis (MS) is one of the most important autoimmune disorders. The characteristic inflammation induces demyelination by damaging myelin sheaths and oligodendrocytes. This process involves injury to the blood-brain barrier (BBB) permeability, which allows entry of lymphocytes (CD8 or CD4 t cells) having affinity to myelin antigens [50]. Depending on clinical presentation, the disease can be active or inactive. If a patient develops signs of relapse with intervals of remission, a diagnosis of relapsing-remitting MS (RRMS) is established. However, some patients may advance towards a progressive disease, referred to as Secondary Progressive MS (SPMS). Increasing disability, regardless of relapses, is a sign of both axonal damage and progression of the pathology [51].

Mast cells (MCs) are found in the brain, the circulatory system, and the GI tract. These immune cells can cross the BBB. It has been demonstrated that MCs can be activated by the gut microbiome, and activated MCs mediate T-cell differentiation by T- T-lymphocytes in favor of Th-1, Th2, and Th17. These helper cells are known as inflammatory phenotypes. Mast cells trigger an inflammatory cascade through proinflammatory cytokines (IL1, IL6, IL8, IL12, IL17, IL23, INF-B, IFN-y, and TNF-a). Recent investigations indicate that MCs degranulation is closely associated with demyelinated plaques in the brains of patients with MS. Murine models of autoimmune encephalomyelitis (EAE) have demonstrated that Inflammatory mediators are expressed during the process of demyelination in both the spinal fluid and the brain. In contrast, MC-deficient mice do not develop EAE. Furthermore, higher levels of inflammatory mediators, such as tryptase, histamine receptor-1, and FceR, are expressed in the cerebrospinal fluid of MS patients. Studies in mouse models show that Tryptase (MCs proteolytic enzyme) activates peripheral mononuclear cells to secrete IL-1, IL-6, and TNF, which stimulate the protease-activated receptor (PAR). This leads to disrupted BBB permeability, myelin destruction, and inflammation [52]. Therefore, MC activation may be a vital contributor to the demyelinating process characteristic of MS.

The NLRP3 Inflammasome is closely intertwined in the pathogenesis of MS. When activated, it triggers a spontaneous oligomerization of NLRP3 with ASC (an adapter molecule), proteolytic activation of Caspase-1 and the release of IL-1B and IL-18. That is, apoptosis-associated speck-like protein (ASC), which contains a caspase recruitment domain (CARD), is a 22 kDa protein that works as the central adaptor for inflammasome assembly [53]. Early progression of the disease is closely related to IL-B, which promotes the opening of both the BBB and the blood-spinal cord barrier (BSCB). This allows entry of immune cells into the cerebrospinal fluid and the brain parenchyma. Therefore, the damage observed in MS arises from the involvement of IL-B in the inflammation-driven neurodegenerative process. Additionally, excitatory neurotransmitters, such as glutamine, induce neural physiology and excitatory postsynaptic currents (EPSCs). However, excessive glutamine signaling and accumulation at synapses can lead to neuronal hyperactivation and excitotoxicity [54].

Alterations in GM have been demonstrated in patients with MS as compared to healthy subjects. In a study using 16srRNA sequencing, downregulation of *Butyricimonas* and upregulation of *Methanobrevibacter* and *Akkermansia* was observed. These alterations are associated with changes in gene expressions that lead to dendritic cell maturation, NF-kB signaling pathways of circulating T-cells, monocytes and interferon signaling [55]. Therefore, significant differences in GM, in various stages of MS are reported in the literature. Low numbers of 19 different species of bacteria were

identified in patients with RRMS. Fourteen of these bacteria belonged to *Clostridia* XIVa and IV clusters. These microbes can produce butyrate, a compound potentially protective for MS as it could suppress pathogenic T cells. Thus, enhancing remyelination. Oral intake of butyrate has been demonstrated to ameliorate symptoms of MS in animal models [56]. Furthermore, an increase of *A-mucinipila* was reported, which may induce the proliferation of Th1. The study hypothesized that the transition from RRMS to SPMS may result from alterations in GM. This leads to an increase in microbial genes involved in DNA mismatch repair in SPMS as compared to RRMS. Accordingly, a straight correlation with oxidative stress has been demonstrated. A cysteine persulfide ratio, an indicator of oxidation, was considerably elevated in the feces of patients with MS [56].

Furthermore, an increase in the *Streptococcus* genera was observed in the SPMS group in comparison to the RRMS groups. S. *parasanguinis* showed the highest correlation with the severity of SPMS. Additionally, a decrease in microbial carbohydrate metabolism has been demonstrated in the gut of patients with SPMS. Accordingly, a significant reduction of anaerobic species that metabolize carbohydrates to produce SCFAs, hydrogen, and carbon dioxide has also been observed. These alterations may lead to gut-derived hydrogen depletion, known for its antioxidant properties. Murine models have shown that hydrogen transport into the systemic circulation ameliorates brain damage by reducing oxidative stress [56].

Inflammatory and autoimmune diseases have been linked to a decreased production of butyrate. This condition damages the intestinal barrier and promotes inflammation. This is promoting research into alternative treatments for butyrate production. A study performed by Jangi S. and colleagues showed an increase in *Akkermansia* and *Metanobrevibacter* bacteria [55]. These bacteria are known for transforming mucin into SCFA, thus mediating immunoregulatory effects. *Akkermansia* triggers a proinflammatory cascade and is unfortunately associated with mucosal degradation, eventually evolving into intestinal barrier deterioration. However, the group that stands out the most for its ability to synthesize butyrate is the Butyricimonas [50]. These findings make us understand the complexity of microbial interactions in the context of autoimmune diseases, providing the basis for future therapeutic investigations. Although the exact mechanism of action between GM and MS remains unknown, there is a clear connection between the disease and the host microbiome (Table 1).

Table 1 Correlation Between Disease, Gut Microbiota and Neurotransmitters.

Disease	***Gut Microbiota (Involved)***	***Neurotransmitter***	***Interpretation (How it works)***
Parkinson´s Disease (PD)	• Escherichia coli • Permeability and inflammatory responses	• α-synuclein (*α*-syn) • Dopamine • Inflammatory cytokines	*α*-syn has a role in the supply and release of dopamine. Gut dysbiosis causes an*α*-syn aggregation in enteric nerves. Tissue storage of this protein injures enteric neurons and has been associated with GI tract dysfunction [2, 5, 22].

Alzheimer's Disease (PD)	**Decreased:** • *Firmicutes* • *Bifidobacterium* • *Escherichia rectale* **Increased:** • *Bacteroidetes* • *Escherichia* • *Shigella*	• Amyloid like proteins • LPS • GBA • Inflammatory cytokines • Tau protein	Amyloid plaques and tau proteins suggest gut dysbiosis. This triggers its pathogenesis that results in inflammation and impairment of the BBB and gut permeability. This leads to LPS translocation and inflammation [20, 47].
Multiple Sclerosis (MS)	**Decreased:** • *Butyricimonas* • *Clostridia* **Increased:** • *Methanobrevibacter* • *Akkermansia* • *A-mucinipila* • *Streptococcus*	• Butyrate production • Immunoregulatory effects • Mucosal degradation • Proliferation of Th1 cells • More severe SPMS	Downregulation of bacteria clusters with anti-inflammatory properties, such as SCFA, and neurotransmitters production. Upregulation of pro-inflammatory bacteria. This changes lead to gut dysbiosis and increased gut permeability, which are associated with poor neuronal processes and neuroinflammation. These represent the main characteristic of neurodegenerative diseases [50-56].
Anxiety	**Decreased:** • *Butyricicoccus* • *Sutterella* • *Eubacterium rectale* • *Faecalibacterium* • *Lachnospira* **Increased:** • *Enterobacteriaceae* • *Desulfovibrio* • *Enterobacterales* • *Eggerthella*	• SCFA production • Mucosal integrity by Butyrate production • Decreased cytokine-proinflammatory-related activity • Pro-inflammatory activity	An inflammatory state is produced as a consequence of decreased gut microbiome taxa. Accordingly, anti-inflammatory molecule production, such as SCFA, butyrate, and neurotransmitter synthesis develops. There is an increase in inflammatory bacterial population [41-46].
Bipolar Disorder (BD)	• *Clostridium perfringens* • SCFA **Decreased:** • *Coprococcus* • *Faecalibacterium* • *Streptococcus*	• Proinflammatory biomarkers: IL-6, IL-1B, IL-2, NF-kB, TNF-*α* • Serotonin • LPS • Monooxygenase	Cytokines decrease the level of serotonin. The imbalance of tryptophan, serotonin and Kyn metabolism impact BD; tryptophan is metabolized through microbiota [8, 29-39].

- *Eggerthella*

α-syn, α-synuclein; TAU, tubulin associated unit; SPMS, secondary progressive multiple sclerosis; SCFA, short chain fatty acids; BBB, blood-brain barrier; LPS, Lipopolysaccharides; GABA, Gamma-aminobutyric acid; Th1, Type 1helper, Kyn, Kynurenine; BBB, Blood-Brain Barrier; IL, Interleukin; NF-KB, Nuclear factor kappa B; TNF-α, Tumor necrosis factor - alpha.

7. Nutrition

7.1 Probiotics

Dietary modulation is a mechanism that can regulate the function and structure of GM. Different nutrients or supplements improve gut dysbiosis by enhancing the growth of beneficial bacteria. These foods, known as "Probiotics", are living organisms that provide valuable health effects depending on the amount and specific strain delivered [57, 58]. The positive response of the organism to probiotics has to do with a direct interaction of bacteria with epithelial and immune cells [59]. Other mechanisms by which probiotics confer beneficial effects are producing organic acids and SCFA. These compounds are significantly involved in the gut-brain axis [19]. Probiotics are found in fermented food products. Their lactose contents allow for the growth of bacteria. However, products such as kombucha, sauerkraut, or kimchi have not been proven to be of benefit yet. Studies show they no longer contain live microbes after fermentation [58]. For this reason, probiotic supplements have been developed in different formulations/presentations, including capsules, powders, tablets, or fluids to facilitate their swallowing. Scientific researchers use specific dosages and strains as either treatment or modulation of symptoms in different conditions [60]. Whether the prognosis improves depends on the host response and the probiotic utilized.

7.2 Prebiotics

Prebiotics refer to non-digestible and fermentable substrates that, in proper environments, contribute to the growth of selective microbial taxa. Consequently, they change both GM composition and activity in the colon. These food ingredients mostly include specific types of oligosaccharides that are resistant to human digestive mechanisms. Some of them are inulin, oligofructose, and fructooligosaccharides, among other polysaccharides [61]. Specific strains of bacteria may further ferment these compounds. They include saccharolytic microbes, such as beneficial Bifidobacteria [62]. This fermentation process results from probiotic bacteria colonization and indirect SCFA production [63]. SCFAs produced mainly include butyrate, acetate and propionate, which have a variety of properties [61]. Butyrate may mediate neuroimmune mechanisms by triggering T-regulatory cells while decreasing proinflammatory cytokine gene expression. It can also work as an inhibitor of histone deacetylases [62].

Specifically, inulin-type fructans have been shown to increase the production of SCFAs by 30%. This rise is mainly represented by propionate and butyrate. They have also been demonstrated to increase the secretion of anti-inflammatory cytokines, like IL-2 and IL-10. Prebiotics such as agave fructans have been shown to increase the secretion of glucagon-like-peptide-1, which may impact the brain's glucose metabolism. This physiologic response has been demonstrated to exert neuroprotective effects [63]. Nonetheless, health-beneficial effects depend on the host's microbial diversification and the metabolites produced rather than prebiotics by themselves [61].

7.3 Psychobiotics

The original definition of psychobiotics included "probiotics", which confer mental health benefits through interactions with commensal gut bacteria. This concept has been extended to include "prebiotics" [64]. Both probiotics and prebiotics have been shown to lower systemic inflammation and improve the BBB integrity [63]. They enhance the cortisol triggering response (marker of emotional disorders), modulate neural pathways associated with emotional awareness, and improve mood and neural function [62]. The mechanisms by which bacteria act as psychobiotics have not been fully understood. However, current evidence indicates that their beneficial effects involve modulating HPA stress response and reducing systemic inflammation. Studies have demonstrated a direct impact on the immune system as well as the secretion of all neurotransmitters, proteins and SCFAs [64]. Different oligosaccharides and species of Lactobacillus and Bifidobacterium bacteria are involved in these processes. They have been investigated as potential probiotics. Their possible underlying mechanisms have been studied in rodents and human trials [65].

8. Conclusion

Different communication pathways between the gut microbiome (GM) and the brain have been described from a biomolecular perspective. This interaction has been associated with the pathogenesis and development of different neurodegenerative diseases. The gut-brain axis (GBA) is key in this molecular connection. The Blood Brain Barrier (BBB) may carry Mast cells (MC), Amino acids, and Cytokines, among other components. MC can activate Treg, Th2, Th17, and Th2 lymphocytes, which trigger the inflammatory cascade. The vagus nerve connects the gut to the central nervous system, specifically to the nucleus of the solitary tract of the brain, via sensory signals. Activation of the Hypothalamus-Pituitary-Adrenal (HPA) axis from a stress response releases cortisol in the circulatory system. Activated immune cells release cytokines that cause changes in the bacterial composition of the microbiome. Gut microbiomes synthesize metabolites and neurotransmitter precursors from the diet. Many of the precursors are amino acids. Glutamate, GABA, Dopamine and SCFAs are metabolites that impact bowel motility, secretion, and inflammation. Up to 90% of serotonin (5-HT) is synthesized in the gut epithelium, and SCFAs modulate it. Gram-negative bacteria produce lipopolysaccharides (LPS), which are recognized and bound by TLR4, subsequently triggering pro-inflammatory cytokines. In this review, we analyze current evidence on transcription, changes in composition, and specific interactions between the gut and brain from the "Biomolecular" perspective. Weaknesses of this review include the lack of studies dealing with clinical presentation and treatment alternatives for neurodegenerative diseases.

9. Take-home Message

From the information reviewed here, we understand that gut microbiome is key to optimal human health. Modulation of immunity, metabolism, and the nervous system are some of the primary roles of GM. Any imbalance in the microbiota (Dysbiosis) triggers the innate immune system. Inflammasomes and immune cells are subsequently activated, which leads to a pro-inflammatory cascade. This process has been implicated in the development of different neurodegenerative

disorders. Gut-brain axis interaction has been involved in neurodegeneration and progression of Parkinson's Disease, Alzheimer's Disease, Multiple Sclerosis, and Mood Disorders, among others. Future lines of research should concentrate on trying to further understand this gut-brain interaction and the complexity of Gut Microbiome from the clinical and the biomolecular view. Studies modulating dysbiosis could result in successful preventive and treatment strategies for neurodegenerative diseases.

List of Abbreviations

5-HT	*5-hidroxytriptamine*
α-syn	*Alpha-synuclein protein*
AD	*Alzheimer's Disease*
ALS	*Amyotrophic lateral sclerosis*
AIE	*Autoimmune encephalitis*
BD	*Bipolar Disorder*
BP	*Blood pressure*
BDNF	*Brain-derived neurotrophic factor*
CNS	*Central nervous system*
TCD8	*Cytolytic T Lymphocyte*
DNA	*Deoxyribonucleic acid*
ENS	*Enteric nervous system*
ECCs	*Enterochromaffin cells*
GABA	*Gamma-aminobutyric acid*
GI	*Gastrointestinal*
GD	*Gut dysbiosis*
GM	*Gut Microbiome*
HPA	*Hypothalamic-pituitary-adrenal*
IL-1α	*Interleukin-1 alpha*
IL-1B	*Interleukin-1 beta*
IL-6	*Interleukin-6*
Kyn	*Kynurenine*
LB	*Lewy bodies*
LPS	*Lipopolysaccharides*
TCD4	*Lymphocyte helper T cell*
MCs	*Mast cells*
KMO	*Monooxygenase*
MS	*Multiple Sclerosis*
RRMS	*Multiple Sclerosis: Relapsing-Remitting MS*
EAE	*Murine autoimmune encephalomyelitis*
ND	*Neurodegenerative diseases*
NF-κB	*Nuclear factor kappa-light-chain-enhancer of activated B Cells*
OS	*Oxidative stress*
PD	*Parkinson's Disease*
RRMS	*Relapsing Remitting MS*

SCZ	*Schizophrenia*
SPMS	*Secondary Progressive MS*
SCFAs	*Short-chain fatty acids*
BBB	*The blood-brain barrier*
TLR4	*Toll-like receptor-4*
TPH1	*Tryptophan hydroxylase 1*
TNF-*α*	*Tumor necrosis factor - alpha*
Th1	Type 1 helper

Author Contributions

All authors contributed equally to the conception, literature review, drafting, the overall content and revising of the article. We all approved the version of the manuscript to be published.

Competing Interests

The authors have declared that no competing interests exist.

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