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Microbiome-Driven Neurobiology Understanding of the Gut-Brain Communication Network

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Abstract: The human gut microbiome is an extremely multifaceted and dynamic ecosystem that includes bacteria, viruses, fungi, and archaea that interact to play fundamental roles in host physiology, metabolism, immunity, and neurodevelopment. Since its first identified in the nineteenth century by cultivation-based methods, microbiome research has expanded and is now supported by the 16S rRNA sequencing method, metagenomics, culturomics, and multi-omics platforms, which allow the researcher to gain a deeper insight into microbial diversity and functional interactions. In healthy individuals, the predominant bacterial phyla, Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, play a role in the regulation of metabolism, synthesis of nutrients, and intestinal integrity. The gut-brain axis (GBA) has become an important two-way communication system that connects the gastrointestinal tract with the central nervous system via the neural, endocrine, immune, and metabolic systems. Gut microbial dysbiosis has been implicated in a growing number of neurological and neurodevelopmental diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and autism spectrum disorder Ne.w therapeutic approaches to the microbiome, which include probiotics, prebiotics, synbiotics, psychobiotics, and fecal microbiota transplantation (FMT), show the potential to restore the microbiome, reduce inflammation, and control neurochemical signaling.. Multi-omics data integration provides a holistic system of connectivity between microbial genetic potential, real-time metabolic expression, and host phenotypes, enhancing mechanistic insights into microbiome-host interactions. Altogether, the microbiome-gut-brain axis is a paradigm shift in human health, and the gut microbiota is a key player that regulates brain activity and pathology.

Keywords: *Gut Bacteria, Human Health, Neurological Disorders, FMT, Probiotics, Metabolomics.*

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I. INTRODUCTION

After the discovery of gut microbiota in the 19th century, research progressed from isolation and cultivation to 16S rRNA gene sequencing and eventually moved toward combining metagenomics and culturomics techniques (Bellali: Running after ghosts: are dead bacteria... - Google Scholar). The gut microbiome is a complex collection of microorganisms, including bacteria, viruses, fungi, and archaea, that inhabit the human gastrointestinal system. With thousands of species and trillions of cells, this microbial community is incredibly diverse, and its total genetic content far exceeds that of humans. Beginning at birth, the gut microbiota changes over the course of a person's life according to various factors, including age, diet, genetics, environment, and exposure to antibiotics. Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria are the predominant bacterial phyla in the gut of healthy adults and play crucial roles in preserving host homeostasis (Gomaa, 2020).

The gut-brain axis is a complex two-way communication pathway that employs metabolic, immunological, endocrine, and neurological pathways to interrelate the central nervous system (CNS) with the gastrointestinal (GI) tract and its resident microbiota. This two-way signaling between the gut and brain is facilitated by the vagus nerve, enteric nervous system, microbial metabolites (e.g., short-chain fatty acids), and immune mediators. This is because gut microbes have a major impact on brain function and behavior, as well as control digestive functions. With the development of microbiome science, the notion of the gut-brain axis has changed significantly, and it can be considered a paradigm shift, that is, the transformation of the CNS and GI tract as distinct systems into the interdependent parts of an integrated physiological network (Poojara et al., 2022).

II. THE ARCHITECTURE OF HEALTH: DIVERSITY, STABILITY AND THE GUT-BRAIN AXIS

Defining the microbiome in healthy participants is an essential initial step towards understanding how the microbiome affects health and disease. The gut microbiota (GM) is a group of bacteria, archaea, and eukarya that

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colonize the gastrointestinal tract. The GM is made up of two minor phyla (Verrucomicrobia and Fusobacteria) and four major phyla (Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria).(Eckburg et al., 2005)

Normal healthy individuals are usually hosts of more than 1,000 diverse bacterial types of a small set of dominant phyla, the most common being Firmicutes and Bacteroidetes (Lozupone et al., 2012). To explain microbial diversity in healthy individuals, researchers have attempted to discover certain stable attributes of microbial populations in the human population (Arumugam et al., 2011). Using data provided by the Human Microbiome Project (HMP), the statistical analysis of the distribution of various bacterial species has been used to determine the type of community in specific body locations (Ding and Schloss, 2014). Four different stool community types were identified, and factors such as breastfeeding, sex, and education were linked to these community patterns. Interestingly, although there were differences in particular taxa, there were community types that were predictive of the oral cavity and fecal samples. A longitudinal cohort of 37 healthy American adults not receiving antibiotics showed that over 70 percent of the fecal bacterial species became stable within a period of one year, with few changes further evolving after five years (Faith et al., 2013). The gut microbiota is important for the digestion and nutrition of the host, as it synthesizes nutrients that the host is unable to digest. For example, the capacity of some Bacteroides species to degrade xyloglucans is associated with a particular genomic region. Xyloglucans are often present in vegetables, including lettuce and onion (Larsbrink et al., 2014). Interpretation of the public metagenomic databases showed that 92 percent of people harbored at least one of these relatively rare Bacteroidetes Bactera species with the capability to degrade xyloglucans, which underscores not only the rarity of this nutritional characteristic in the phylum Bacteroidetes but also its relevance to the human host. The results emphasize the symbiotic and co-evolutionary interdependence between humans and their gut microbiota and have significant implications for the field of nutrition and dietary science (Shreiner et al., 2015). There are three main physiological pathways of gut-brain (GBA) communication: neuroendocrine, immunological, and neurological. Communication occurs via the emission of bioactive compounds, quorum-sensing molecules, and microbial secondary metabolites. The physiological nature of GBA signaling and its applicability to central nervous system disorders have been widely outlined, as well as the central scientific mediators of this two-way communication (Lu et al., 2024).

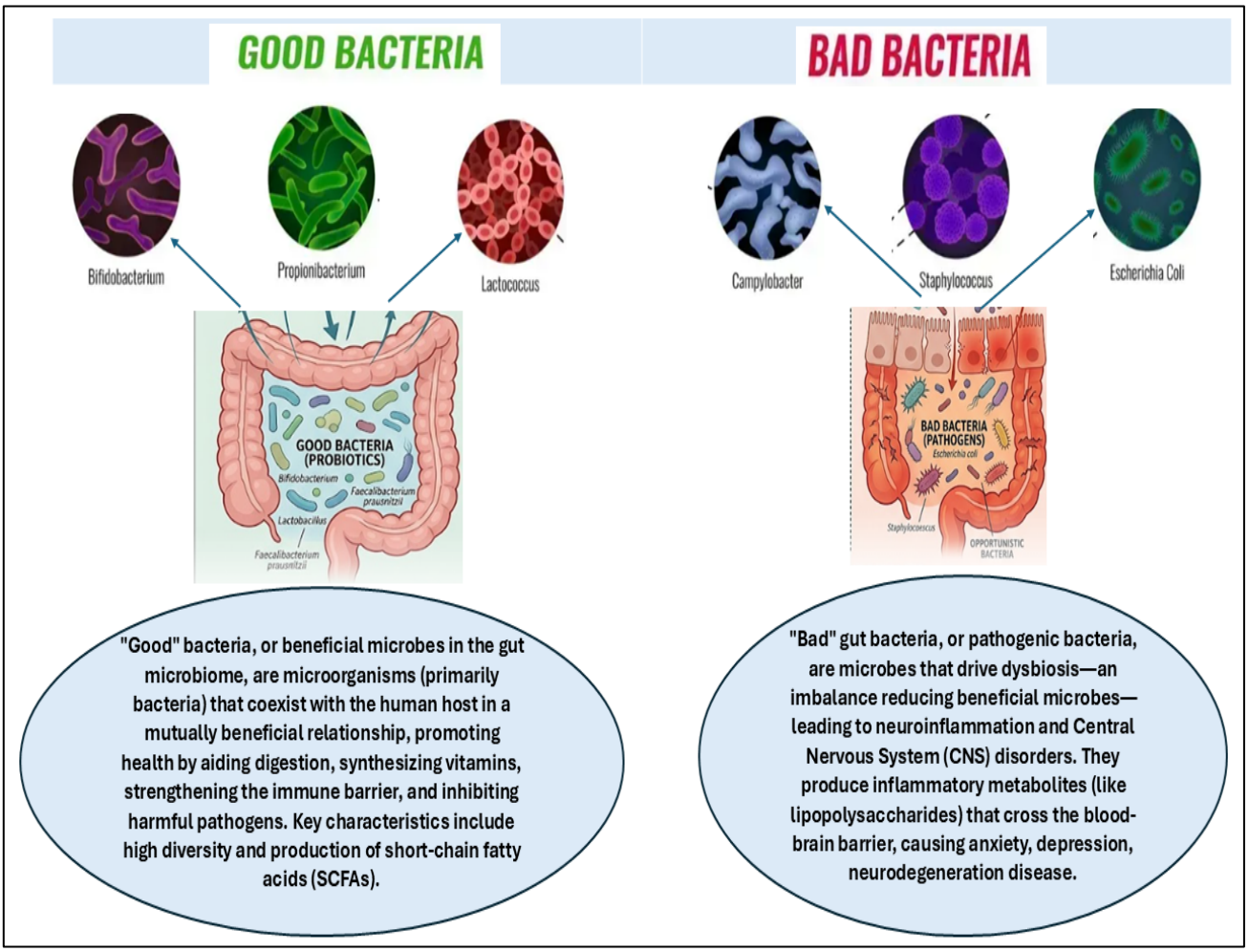

Fig 1 Functions performed by Beneficial and pathogenic gut bacteria in the host. The left figure shows the functions of "Good Bacteria" (probiotics), for instance, Bifidobacterium, Propionibacterium, and Lactococcus.

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Beneficial bacteria form a symbiosis with the host through the formation of SCFAs, the production of vitamins, and strengthening the immune barrier. The right figure demonstrates "Bad Bacteria" (pathogens/pathobionts), for example, Campylobacter, Staphylococcus, and E. coli. Pathogenic bacteria cause dysbiosis, which is the process of generating inflammatory molecules like LPS. They can enter into the brain through blood circulation due to breaching the BBB and lead to neuroinflammation, leading to anxiety, depression, and neurodegenerative disorders.

- *Autonomic Nervous System*

Gut-brain communication is a bidirectional communication system. Brain signals to the gut are mainly conveyed through the autonomic nervous system and hypothalamic-pituitary axis, which controls various physiological processes. On the other hand, gut-brain neural communication is regulated by vagal and spinal afferent neurons. Although spinal afferents supply the gut, their contribution to energy and glucose homeostasis was traditionally viewed as subordinate to that of the intestinal afferents. However, recent data have indicated that spinal afferents play a role in intestinal glucose sensing (Wachsmuth et al., 2022). The tenth cranial nerve, called the vagus nerve, connects the brain to the abdomen and controls internal organ activities, including digestion, heart rate, and breathing rate. The vagus nerve is a combination of efferents and afferents that carries motor messages from the brain to the body, and the gut microbiota can influence intestinal cells. Thus, the brain can sense the gastrointestinal ambience (Agostoni et al., 1957). Vagal afferent terminals are spread across several layers along the gut wall, and many of these nerves target the lamina propria in proximity to enteroendocrine cells (EECs). Despite vagal afferent neurons (VANs) innervating the entire GI tract, recent discoveries have shown that VANs are extremely heterogeneous, with complete subpopulations concentrated in certain areas of the GI tract (Bai et al., 2019). VANs are activated in the gut by two major mechanisms: chemoreception and mechanostimulation. The main type of chemical stimulus is taken by vagal mucosal endings, and GI stretch and distention are taken by intraganglionic laminar endings (IGLEs) (Berthoud and Patterson, 1996). Gastrointestinal secretions of EECs contain peptides that interact with many VANs receptors to demonstrate the relevance of the receptors in the maintenance of energy balance and glucose homeostasis. Developments in the process of neuronal identification and targeting have also clarified the physiological roles of VAN subtypes. Recent studies have proposed the existence of over ten different types of neuronal populations in the nodose ganglion based on protein and receptor expression profiles, but certain results have not been constant (Kupari et al., 2019).

- *Endocrine (Hormonal) Pathway*

The cerebral-intestinal axis is regulated by neurological, endocrine (where the hypothalamic-pituitary-adrenal [HPA] axis plays a major role), and immunological mechanisms. HPA axis modification by immunomodulation mostly occurs through cytokine-mediated transfer. Conversely, neural control is controlled to a great extent by the autonomic nervous system, which consists of the vagus nerve, afferent and efferent fibers, and the enteric nervous system (ENS). Gershon (2003) is credited with having described the ENS, also known as the gut brain, in detail. It has direct control over motility, secretion of the digestive tract, and blood flow. This is a complicated network composed of a large number of related nerve fibers that use over 30 different neurotransmitters. Each intestinal villus contains approximately 40 neurons (Breit et al., 2018). The glial cells under the ENS neurons also differ in the peripheral nervous system, as they are of the astrocyte type, similar to the central nervous system (CNS), and not Schwann or collagen.

The ENS comprises two main plexuses, the Meissner (submucosal) and Auerbach (myenteric) plexuses, which are located between the circular and longitudinal muscle layers (Pardo et al., 2020). This anatomical position allows tight communication between the mucosa-associated lymphoid tissue (MALT) and gut-associated lymphoid tissue (GALT) using several neurotransmitters and cytokines. ENS neurotransmitters activate lymphocytes and Peyer's patches receptors. The GALT is a very important part of mucosal immunity, as it hosts approximately 70 percent of all immune cells in the body (Franco-Robles et al., 2019). Moreover, intestinal microbes, such as some bacterial and fungal populations, also interact with both GALT and ENS by generating and releasing neurotransmitter-ressembling substances (Chen et al., 2021). The HPA axis, or stress axis, is the main hormonal governor of communication between the gut and brain and coordinates the stress response. Corticotropin-releasing hormone (CRH) and vasopressin release by the hypothalamus stimulate the anterior pituitary gland to produce adrenocorticotropic hormone (ACTH), which moves through the blood to the adrenal cortex, inducing the release of glucocorticoids, the major one being cortisol (Yamamoto and Kaur, 2025).

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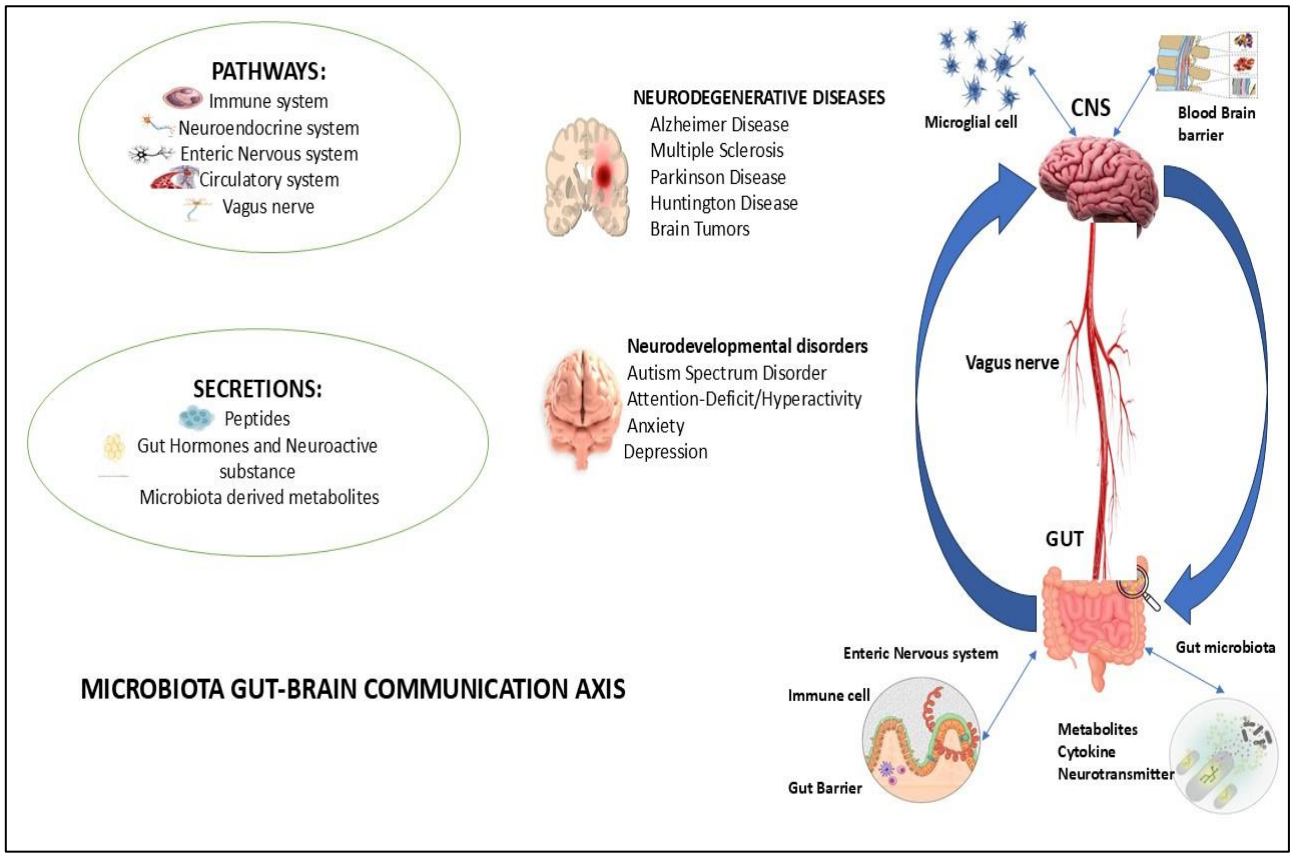

Fig 2 The Microbiota-Gut-Brain Axis

Its Bidirectional Nature and Clinical Applications. The figure demonstrates how the gut microbiome interacts with the central nervous system through different mechanisms, including vagus nerve stimulation, circulation, and immune responses, as well as chemical messengers like metabolites, cytokines, and neurotrophic factors. Disruption of the gut-brain axis has been associated with diverse pathologies, including neurodegeneration (Alzheimer's and Parkinson's disease) and neuropsychiatric illnesses (Autism Spectrum Disorder, Anxiety, and Depression). In the right-hand side figure, the physiological elements of this axis are depicted, such as the blood-brain barrier, microglia activation, enteric nervous system, and gut barrier.

➢ *Immune Pathway*

Brain-gut interactions and health are associated with complex immunological processes. These processes involve immune mediators (mainly cytokines and chemokines) and are important signaling molecules in the inflammatory response. The cytokines involved are interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a), which control the activity of immune cells and the level of inflammatory reactions. The binding of these cytokines to certain receptors triggers intracellular signaling cascades, such as the NF-KB and JAK–STAT pathway,s and eventually alters gene expression and cell behavior. The roles of these pathways are supported by substantial experimental evidence. The activation of the JAKST pathway has been studied in vitro, showing a direct association between cytokine-to-receptor binding and subsequent changes in the phosphorylation state of STAT, as well as gene expression changes (Petrut et al., 2025). In addition, it was demonstrated in vivo that JAK inhibitors can significantly suppress inflammatory signatures and disease severity in animal models of pharmacological blockage of JAK signaling .These results confirm the close correlation between pathway activation and inflammation. In the case of gut inflammation, a high level of cytokine production plays a role in local inflammation of the intestines and systemic immune activation. Pro-inflammatory cytokines can either cross the blood-brain barrier (BBB) or indirectly evoke the CNS via circulation in the body, thus contributing to neuroinflammation. Chemokines also control the recruitment of inflammatory cells to inflamed tissues, and their malregulation may worsen gut and systemic inflammation. It has been shown to be closely linked to neuroinflammatory alterations in the brain, in regions of the brain that regulate mood and behavior, including the hippocampus and amygdala, and in chronic gut inflammation, including inflammatory bowel disease (IBD) (Jia et al., 2025b).

➢ *Metabolic Pathways*

- *Microbial Metabolites*

Short-chain fatty acids (SCFAs) are microbial metabolites formed as a consequence of anaerobic fermentation of dietary fibers by bacteria (Morrison and Preston, 2016). SCFAs are carboxylic acids with aliphatic chains composed of one to six carbon atoms. Acetate, propionate, and butyrate account for more than 95% of the total SCFAs, and lactate occurs in small quantities

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(O'Riordan et al., 2022). Several bacterial genera synthesize SCFAs, including Clostridium, Eubacterium, Fusobacterium, Butyrivibrio, Megasphaera elsdenii, Mitsuokella multiacida, Rosburia intestinalis, Faecalibacterium prausnitzii, and Eubacterium hallii (Mirzaei et al., 2021). Butyrate is one of these metabolites and is the major energy source for colonocytes, and is essential for cellular growth, differentiation, and epithelial integrity (Pituch et al., 2013). SCFAs also play a role in maintaining intestinal barrier function and in the growth of beneficial microbiota (Hoffman et al., 2019). Moreover, SCFAs regulate the inflammatory process by lowering the secretion of interleukin-8 (IL-8) and inhibiting proinflammatory signaling pathways in the intestinal epithelium (Li et al., 2018).

- *Tryptophan Metabolism*

Indole, serotonin, and melatonin synthesis as a result of tryptophan metabolism by gut microorganisms might decrease the supply of tryptophan to the host, since tryptophan is an essential amino acid (Martin et al., 2018). Pseudomonas species synthesize serotonin using tryptophan and use it to signal and toxicate intercellularly. Tryptophan metabolism by the gut microbiota influences the production of tryptamine through tryptophan decarboxylase, and the resultant drop in the blood levels of tryptophan affects the activity of serotonergic transmission and the functioning of the central nervous system (CNS) and enteric nervous system (ENS) (Jenkins et al., 2016). Tryptamine alters the inhibitory effect of enterochromaffin cells on serotonin by enhancing the release of serotonin by enterochromaffin cells (Williams et al., 2014). Various indole derivatives and neuroactive compounds, such as kynurenine, quinolinate, indole, and various indole derivatives, are produced by the gut microbiota, and all of them affect brain facilitation and behavior (Gao et al., 2018). Kynurenine and quinolinate have the potential to induce changes in brain activity, which helps in the depletion of host tryptophan and the symptoms of depression (Oxenkrug, 2013). Kynurenine synthesis and quinolinate decrease the amount of tryptophan in circulation and restrict the amount of central serotonin production (Waclawiková and El Aidy, 2018). In addition, indole and its analogs, including indole acetic acid (IAA) and indole propionic acid (IPA), affect the metabolism of the central nervous system (CNS) (Jaglin et al., 2018). Thus, tryptophan catabolism-associated microbiota is a significant modulatory process in the gut-brain axis. Neurotransmitters Modulated by the Gut Microbiota and Synthesized. Recent studies suggest that, in addition to short-chain fatty acids and bile acids, the gut microbiota generates metabolites, including neurotransmitters of glutamate, gamma-aminobutyric acid (GABA), serotonin, and dopamine (P, 2018). Some bacteria have genes that encode enzymes that can catalyze the conversion of their substrates to neurotransmitters or their precursors (Luqman et al., 2018). Moreover, bacterial metabolites have the potential to act as signaling molecules that activate the production and release of neurotransmitters in enteroendocrine cells (Yano et al., 2015). Glutamate, GABA, dopamine, and serotonin neurotransmitters cannot cross the blood-brain barrier (BBB) and are produced in the brain from circulating precursors. These precursors are mostly dietary amino acids, such as tyrosine and tryptophan, which are absorbed into the bloodstream, cross the BBB, and are absorbed by neurons. The precursors are then transformed into functional neurotransmitters through a series of enzyme reactions, such as serotonin, norepinephrine, and dopamine. Therefore, the gut microbiota can control the behavior of the host indirectly by modulating the metabolism and supply of neurotransmitter precursors (Chen et al., 2021)

III. RELATIONSHIP BETWEEN THE GUT MICROBIOME AND NEURODEGENERATIVE DISEASES

➢ *Alzheimer disease (AD)*

Alzheimer's disease (AD) is a neurodegenerative disease affecting the central nervous system, which is progressive and contributes to approximately 6080 percent of the dementias that occur (Hu et al., 2016). AD is clinically manifested by gradual memory loss, cognitive dysfunction, language disorder, and decreased activities of daily living (Scheltens et al., 2021). The pathology of AD is characterized by two principal signs: extracellular amyloid-9 (A) amyloid plaque deposition and intracellular neurofibrillary tangles due to hyperphosphorylation of tau protein (Dubois et al., 2021). These pathogenic deposits cause neuroinflammation, synaptic dysfunction, and neuronal loss (Kohler et al., 2016). One clinical study found that Escherichia/Shigella abundance was increased and Eubacterium rectale and Bacillus subtilis abundance was decreased in patients with amyloid-positive AD relative to controls, indicating that amyloid deposition and related microbial changes both contribute to cognitive impairment (Cattaneo et al., 2017). Some intestinal microbiota species, such as B. subtilis and Escherichia coli, produce large amounts of lipopolysaccharides (LPS) and amyloid proteins (Mancuso and Santangelo, 2018). These microbial products can directly enter age- or disease-weakened intestinal and blood-brain barriers or indirectly trigger pro-inflammatory cytokines and other mediators, contributing to AD pathogenesis (Jiang et al., 2017). The gut microbiome of patients with AD is usually characterized by a higher prevalence of pro-inflammatory taxa and a lower abundance of butyrate-producing microorganisms, which regulate immunity and have anti-inflammatory effects. Thus, one of the possible therapeutic approaches to AD is restoring the homeostasis of the intestines by decreasing the activity of pro-inflammatory microorganisms on the one hand and increasing anti-inflammatory metabolism, on the other hand (Haran et al., 2019).

➢ *Parkinson's Disease (PD)*

The second type of neurodegenerative disorder is Parkinson's disease (PD) that is seen in about 1–4% of people above 60 years of age globally (Tysnes and Storstein, 2017). The three main pathological characteristics of PD are (1) deposition of alpha-synuclein in the dopaminergic neurons of the brainstem and substantia nigra pars compacta (SNpc) (Hrvolová et al., 2016); (2) gradual disappearance of the dopaminergic neurons (Pitton Rissardo et al., 2025); and (3) prion-like transneuronal spread of alpha-synuclein

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pathology (Braake et al., 2003). PD has motor signs, including resting tremor, rigidity, and bradykinesia, and non-motor signs, including gastro intestinal and constipation, depression, urinary problems and impaired thinking (Jankovic, 2008). The α-synuclein is a monomeric protein, which is unfolded, and soluble in its native form. It is misfolded into structures rich in β-sheets by different factors, such as environmental toxins (Stefanis, 2012), oxidative stress (Puspita et al., 2017), and genetic mutations (Kasten and Klein, 2013). These form oligomers and protofibrils and later become insoluble fibrils (Ghosh et al., 2017). Lewy bodies (LBs) and Lewy neurites (LNs) are the accumulations of mature fibrils in the dopaminergic neurons of the SNpc that results in neuronal degeneration (Irwin et al., 2013). Within the last 20 years, about 28 rare and monogenic familial varieties of PD have been linked to 28 genes or loci (Gasser, 2009; International Parkinson's Disease Genomics Consortium (IPDGC) et al., 2014). The majority of the cases of PD are however sporadic and are probably due to gene environment interaction (McCormack et al., 2002). The gut microbiome together with its metabolite have received an increased focus of attention among environmental factors. The gut-brain axis role in the pathogenesis of PD goes back to the observation of Lewy pathology in the enteric nervous system (ENS) in the 1980s (Qualman et al., 1984). Since that time both top-down (brain-to-gut) and bottom- up (gut-to-brain) models of α-synuclein propagation have been suggested.

- *Multiple Sclerosis (MS)*

Multiple sclerosis (MS) is a chronic autoimmune disorder that afflicts millions of people in the world especially in the northern parts. Succession of the disease is characterized by the gradual loss of the quality of life associated with immune-mediated destruction of myelin sheath, the insulating layer of spinal cord axons (Dendrou et al., 2015). Demyelination causes the loss of transmission of electrical signals leading to paralysis and other neurological symptoms. The most common type is known as relapsing remitting MS (RRMS) which takes about 85 due to its episodic nature of neurological impairment and then remission. About 6 out of ten people with RRMS ultimately develop a secondary progressive MS (SPMS) which is a progressive and permanent worsening of the nervous system (Plantone et al., 2016). The gut microbiota is significant in disease development and progression of multiple sclerosis (MS), which is an autoimmune neuroinflammatory central nervous system disease that is associated with demyelination and neurodegeneration. MS is always characterized by changes in gut microbial composition (dysbiosis) which can be the cause of immune dysregulation, chronic inflammation, and disease activity as shown in human and animal research (Ordoñez-Rodriguez et al., 2023). Many case-control studies have demonstrated that the gut microbiota of patients with MS is continuing to be dysbiotic relative to the healthy controls. These changes involve the following: Reduced number of SCFA-producing bacteria: Patients with MS often have low levels of Firmicutes and other useful genera, including Roseburia, Coprococcus, Faecalibacterium, and Prevotella. These bacteria are significant producers of the short-chain fatty acids (SCFA), especially butyrate, that is a major contributor in the regulation of immune responses and the integrity of gut barrier (Saresella et al., 2020). Higher abundance of possibly pro-inflammatory taxa: MS cohorts have been reported to have increased abundance of Akkermansia, Blautia, Ruminococcus, and others which might be linked to increased mucosal immune activation and inflammation (Pellizoni et al., 2021).

- *Autism Spectrum Disorder (ASD)*

The term autism spectrum disorder (ASD) includes autism, Asperger syndrome, and severe developmental disorders with no other specifications (De Angelis et al., 2013a). The disorder of ASD is marked by bad communication, social withdrawal, repetitive or constraining patterns of behaviors, and early appearance of the symptoms in the course of development (AP Association: Diagnostic and Statistical Manual... - Google Scholar," n.d.). Other symptoms mentioned are anxiety (Mayer et al., 2014), more aggressive behavior (Manchia and Fanos, 2017), and selective or fussy eating (Dinan and Cryan, 2017). One of the subsets is the regressive (late-onset) form of autism, where children show developmental progression, after which they lose their social interaction and communication skills (De Angelis et al., 2013b). Gut epithelial metabolism and disaccharide absorption is altered in children with ASD (Kang et al. 2013). Less mRNA expression of brush-border disaccharidases, such as lactase, maltase-glucoamylase, and sucrase-isomaltase, has been found in the ileum, which causes a lower level of gene expression (Naviaux, 2014).

Moreover, sodium-dependent glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2) mediate the transport of glucose, fructose and galactose across the enterocyte membranes. Research has claimed an important decline in mRNA expression of both hexose transporters in the ileum of ASD children (Williams et al., 2011). In turn, the compromised absorption will result in high concentrations of monosaccharides and disaccharides in the large intestine. These low-molecular-weight sugars are fermentable by bacteria and enhance the growth of sugar-fermenting bacteria and may upset the polysaccharide-degrading microbes balance. High sugar in the colon can be a factor in causing osmotic diarrhea or high volume of gas, which are typical gastrointestinal (GI) symptoms in ASD. In patients with ASD, bloating and diarrhea are common phenomena. Notably, the severity of GI symptoms has proved to be linked to the severity of autistic behaviors (Iovene et al., 2017a). It has also been reported that augmented intestinal permeability is found in ASD patients, which is evidenced by the upsurge in blood lactulose levels after the administration of this compound orally (Iovene et al., 2017a). Such increased permeability may be explained by the decreased expression of proteins forming barriers and the increased expression of tight-junction pore-forming proteins. There were these changes denoted by the comparison of the samples of the small intestine mucosa of children with autism and their controls (Fiorentino et al., 2016). As Lactobacillus species are reported to facilitate tight junction maintenance of the intestinal epithelial barrier, low concentrations of these bacteria in ASD patients could

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also be an additional cause of the barrier dysfunction (Iovene et al., 2017b). Also, there is a possibility of bacterial metabolites gaining access to the damaged intestinal barrier, changing the levels of cytokines and causing systemic inflammation, which can influence the functioning of the brain (Santocchi et al., 2016).

- *Identification and Description of Gut Microbiome Host Changes*

The precise diagnosis of microbial dysbiosis is a key element in the formulation of specific interventions, and it requires the combination of high-resolution analysis tools to unravel the convoluted community framework and functional interactions in the gastrointestinal tract. This area has been transformed by the use of next-generation sequencing, which allows the culture-independent profiling of bacterial, archaeal, and fungal taxa at a high resolution (Bautista et al., 2025, p. 5). These sequence based metagenomic methods have played significant roles in decoding the composition and dynamics of the gut microbiota whilst the functional approach of metagenomics has been able to discover new functional genes, microbial pathways, and the functional dysbiosis of the gut microbiota (Bashir & Khan, 2022, p. 2). Metatranscriptomic and metabolomic studies can be used to complement genomic data and present essential information on the active microbial metabolic pathways and the neuroactive metabolites, including short-chain fatty acids and neurotransmitters, that support communication along the gut-brain axis. The combination of multi-omics integration, which integrates the results of genomics, transcriptomics, and metabolomics, can provide a complete picture of the microbiome-gut-brain axis by matching the microbial genetic potential with the real functional expression and metabolic activity (Dong and Mayer, 2024; Margoob et al., 2024, p. 13). Although such genomic tools are potent, 16S rRNA gene sequencing can usually perform taxonomic classification at the genus or species level, and shotgun metagenomic sequencing can be used to achieve strain-level resolution and furthermore to obtain more information about how microbial communities can work (Interino et al., 2025). To further clarify the operational dynamics in such communities, metatranscriptomics concentrates on the transcripts of RNA to uncover which genes are in operation hence giving real-time data of the functioning of microbes (Aguiar-Pulido et al., 2016). This practical profiling is crucial in establishing particular microbial pathways linked with the neurological states, and hence the intelligent establishment of specific interventions like synbiotics (Duve et al., 2024). This understanding is further improved by the metagenomic systems biology strategies that create community level metabolic networks to connect bacterial composition to certain host phenotypes by analyzing complicated interactions among microbial parts.

- *Metagenomics*

Metagenomics serves as a strong, community-driven tool for analyzing microbial genomes sourced from ecological niches (e.g., the gut) where microorganisms coexist, to characterize the phylogenetic, physical, and functional attributes of the microbiota, using a culture-independent approach. Recent metagenomics strategies employ the shotgun strategy to deliver a microbial community profile, starting from DNA sequence reads and their alignment to reference genomes(Wilmes and Bond, 2006). Sample processing is the very first step in metagenomics studies. It is essential to ensure that the isolated DNA is representative of all organisms in the sample and that there is enough material to construct a library and carry out sequencing. There are specialized protocols depending on the sample under study, and there are numerous methods of DNA isolation from samples that work well (Burke et al., 2009). In cases where the sample contains a host (for example an invertebrate or plant), fractionation or selective lysis could be employed in order to ensure that there would be minimal host DNA included (Thomas et al., 2010). This is especially crucial in case the host genome was large compared to the genome of the microbial communities, hence possibly "overwhelming" the latter during the subsequent sequencing steps. Physical fractionation could also be applied in cases where just a specific portion of the community needs to be studied, for example viral fractions in seawater. In such cases various methods of selective filtering or centrifuging could be employed, along with even flow cytometry (Palenik et al., 2009).

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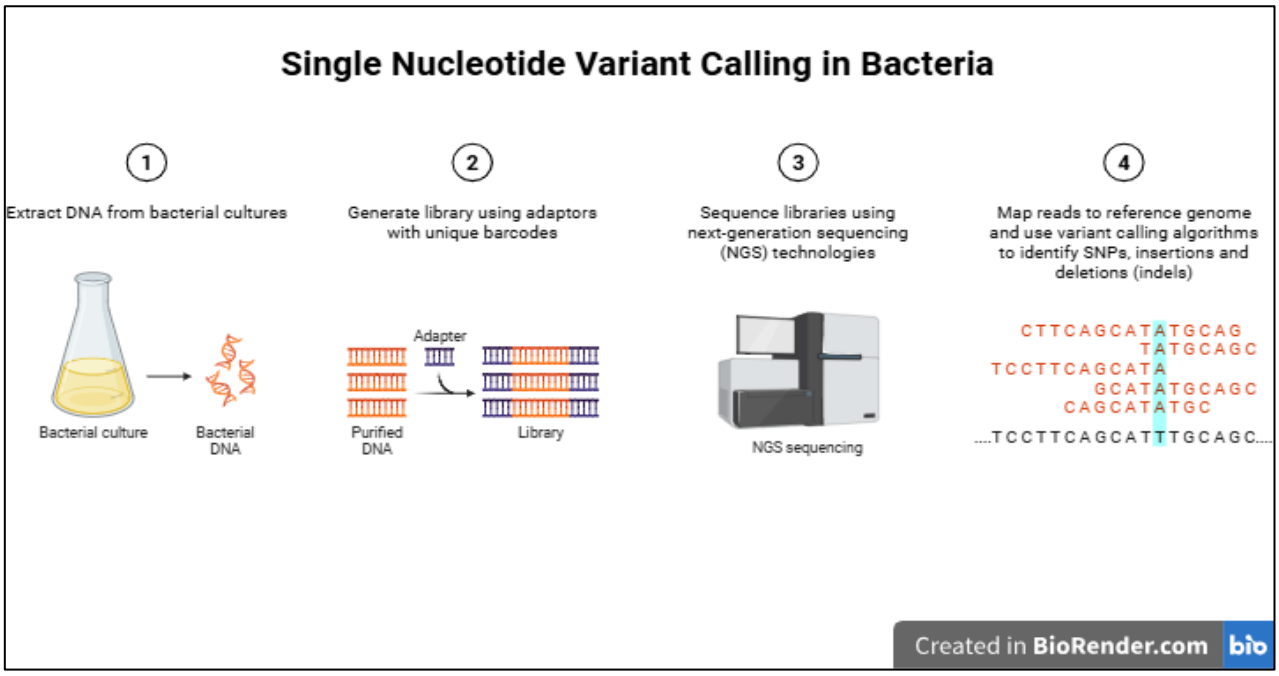

Fig 3 Workflow of Single Nucleotide Variant (SNV) Calling in Bacterial Populations.

The entire procedure can be broken down into four main phases: (1) DNA Extraction: This entails the extraction of high quality genomic DNA from pure cultures of bacteria. (2) Library Construction: The fragmentation of purified DNA and the addition of sequencing adapters and unique molecular identifiers to facilitate pooling samples. (3) Next Generation Sequencing (NGS): This entails the use of an NGS platform to sequence the constructed library; platforms include Illumina and Ion torrent. (4) Bioinformatics analysis: Alignment of sequenced reads to a specific reference genome, then variant calling to detect SNPs and indels. This figure was created with BioRender (https://biorender.com/)

- *16S rRNA Gene Sequencing from a High Genomic Background*

The phylotyping of 16S rRNA genes (Woese and Fox, 1977) as an NGS technology has transformed the research of the human microbiome. The 16S rRNA sequencing technique has enabled an alternative to microbial culture to be just as simple and effective. The 16S rRNA gene encodes a ribosomal subunit, which is highly conserved and present in the bacteria and has hypervariable regions at interdependent position of its sequence(Clarridge, 2004) These hypervariable regions are species-specific, which makes it possible to classify or taxonomize. The conserved regions, however, can be used to develop common primers that attach to known sequences that are present in majority of the bacteria. It can be performed on a specific region of one or a few proximal regions using short read sequencing of about 200-400 base pairs with specific primers that will match the conserved regions on both end of the hypervariable target. Most bacteria are not culturable and that is why NGS is most likely regarded as the most effective method of trying to assess the array of bacteria in a comprehensive manner (Stewart, 2012). Moreover, it has been demonstrated that, with very low abundance taxa in a mixed population, deep metagenomics analysis is insufficient in the terms of read depth and 16S amplification and sequencing using universal 16S primers is needed (Mori et al., 2014). The technical parameters of such NGS studies require PCR sensitivity, extensive taxonomic coverage and the capacity to distinguish well between bacterial 16S rRNA and eukaryotic 18S rRNA genes (Pace, 1997) . Balancing the three is highly challenging to do as the broad-spectrum bacterial 16S primers do not discriminate between bacterial 16S and mammalian 18S rRNA genes. Also, in this case, both forms of sample need amplification of unknown, yet possibly very low concentrations of bacterial targets in an excess of human background DNA. As a point of comparison The Human Microbiome Project Consortium generally use samples collected in non-invasive manner with an up to 80 human genomic aspect (Human Microbiome Project Consortium, 2012).

Table 1 Integrated Multi-Omics Platforms and Representative Bioinformatics Tools Employed for Comprehensive Analysis of Microbial Communities.

Omics Category	Tool Name	Function	Application	Key Features
Biomarker Profiling	Random Forest (ML-based)	Microbiota composition	Biomarker discovery & classification	Combines statistical significance with biological relevance (Knights et al., 2011).
Metagenomics	QIIME 2	Microbiota functional gene capacity	16S rRNA & shotgun data analysis	Modular, reproducible workflows (“Microbiome Analysis with QIIME2,” n.d.)

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Metabolomics	XCMS	Metabolic productivity	LC-MS data processing	Peak detection & alignment (Smith et al., 2006)
Metatranscriptomics	HUMAnN3	Microbial functional gene Expression	Functional activity profiling	Gene expression analysis (Franzosa et al., 2018)
Metaproteomics	MaxQuant	Protein Expression	Protein identification & quantification	High-resolution MS data analysis (Cox & Mann, 2008).

➢ *Targeting Microbiome Therapy with Mechanistic Basis.*

The strategies used to treat gut microbiota are based on a number of biological processes. To begin with, gut-based bacteria produce neurotransmitters like serotonin, gamma-aminobutyric acid (GABA), and dopamine precursors, which affect the neural signaling. Second, dietary fiber fermentation in the small intestine yields SCFAs such as acetate, propionate, and butyrate which control neuroinflammation and vagus nerve function. Third, gut microbes control immune responses and cytokine generation thus affecting neuroimmune interactions (Kezer et al., 2025). SCFAs also increase the blood-brain barrier integrity and neurogenesis by increasing the signaling pathways associated with synaptic plasticity and neuronal survival. Experimental evidence shows that microbiome interventions trigger the enhanced expression of brain-derived neurotrophic factor (BDNF), which is the promising treatment effect of microbiome modulation. The class of agents is known as psychobiotics and can be either probiotic, postbiotic, prebiotic, or synbiotic and activate the gut -brain axis and provide mental health (Dinan et al., 2013). Psychobiotics possess a psychotropic influence on anxiety, depression, and stress (Bravo et al., 2011). Microbes of the brain and gut interact via the vagus nerves, the immunoregulatory processes, and the neuroendocrine system (Li et al., 2018). One of the strategies used by psychobiotics is to influence the cognitive and emotional pathways, the hypothalamic-pituitary-adrenal (HPA) axis of inflammatory molecules directly linked with depression (Dowlati et al., 2010), or to influence the neurotransmitters and proteins that comprise the brain functions (Lu et al., 2008). Human microbes like Lactobacillus GG and Bifidobacterium infantis 35, 624 augment the interleukin-10 and consequently by trimming down pro-inflammatory cytokines either directly or indirectly help preserve the integrity of the blood-brain obstacle (de Vries et al., 1996). Lactobacillus Lactobacillus odontolyticus and Lactiplantibacillus plantarum are strains that produce acetylcholine (Roshchina, 2016). There is also a similar increase of serotonin production by the enterochromaffin cells by spore-forming gut microbes in humans (Yano et al., 2015). Psychobiotics, and primarily, FMT have recorded positive effects when used in management of numerous mental conditions including but not limited to Parkinson disease , Alzheimer disease (Akbari et al., 2016), Tourette syndrome (Zhao et al., 2017), autism (Shaaban et al., 2018a), and insomnia (Nakakita et al., 2016). FMT was established to be effective in alleviating the state of depression and anxiety (Chinna Meyyappan et al., 2020). Therefore, psychobiotics have come as a remedy to all sorts of neurodegenerative disorders. It may be a valuable and promising approach towards healthy well-being. Human studies have not yet been done despite promising results. Additional studies in the field of psychobiotics should be carried out to use it as an alternative treatment in neurodevelopmental and neurodegenerative diseases.

IV. PROBIOTICS

The ability of probiotics, which are live microorganisms to improve health benefits to the host, has been a focus of research in relation to the microbiome-gut-brain axis (“Whelan: Design and reporting of prebiotic and probiotic... - Google Scholar,” n.d.) Psychobiotics, originally defined as probiotics with health benefits to the host achieved through gut-brain interactions, has mood-enhancing effects, reductions in anxiety and depression scores, and improvements in stress reactions. This definition has been broadened to encompass other ways to target the microbiome that could potentially improve brain process (Long-Smith et al., 2020; Sarkar et al., 2016). Certain strains of bacteria have also been shown to reduce inflammation in preclinical models, including an inflammation model caused by a high-fat diet, where Lactobacillus and Enterococcus strains were able to reduce IL-6, TNF-a and IL-1b, but not anxiety (“Ahmadi: A human-origin probiotic cocktail ameliorates... - Google Scholar,” n.d.) Strain specificity is of great importance; in an example, B. longum was able to reduce depression in individuals with irritable bowel syndrome (IBS), but not anxiety in another study (Pinto-Sanchez et al., 2017). plantarum also reduced stress Certain probiotics (e.g. Bifidobacteria and Lactobacilli) have demonstrated potential to improve behavioral and neurochemical impairments in preclinical models of ASD, with Bifidobacteria and Lactobacilli enriching behavioral and neurochemical impairments (El-Ansary et al., 2018); but no significant changes in TNF-a, IL-6, and IL-1b or cortisol were found in any group of probiotics tested in a single study (Shaaban et al., 2018b)

Schizophrenia has been linked with peripheral immune abnormalities, although probiotics have not demonstrated much psychiatric effect. The reduction in von Willebrand factor and the modulation of monocyte chemoattractant protein-1, brain-derived neurotrophic (BDNF), chemokine ligand 5, and macrophage inflammatory protein-1β (“Tomasik: Immunomodulatory effects of probiotic supplement... - Google Scholar,” n.d.) Pathway analysis indicated that the inhibition of the changes in L. rhamnosus and Bifidobacterium animalis supplementation is associated with the decrease of IL-17 cytokines in the regulation of immune and intestinal epithelial cells, as well as involved changes in mon Positive outcomes on anxiety and depression in schizophrenia and elevation of TNF-related activation-induced cytokine and IL-22 in respondents are also observed in open-label studies involving Bifidobacterium breve, but lacking placebo arm (Okubo et al., 2019).

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V. PREBIOTICS

An alternative method of manipulating the microbiome-gut-brain axis is prebiotics, non-digestible substrates specially selected to act upon host microorganisms and allow beneficial microorganisms to flourish. Prebiotics are quite common and are available in a large number of foods such as fruit, vegetables, whole grains and human milk. Prebiotics may also improve gut health and possibly improve mental health by promoting the expansion of beneficial microbes such as Bifidobacterium ("Gibson: Expert consensus document: The International... - Google Scholar," n.d.) Among the most researched prebiotics are FOS and GOS, which have been shown to change the composition of gut microbes and lower stress reactions (Mysonhimer et al., 2023) and a review article has found a three week high dose GOS supplementation can reduce the cortisol awakening response in healthy individuals, indicating that prebiotics could have a role in the regulation of both gut health and mental health (Schmidt et al., 2015). Prebiotics were also capable of modulating in utero VPA-induced changes in a mouse model of ASD by mitigating key microbial taxa, improving intestinal permeability, restoring immune homeostasis, reducing neuroinflammation (reducing CD68 expression, in particular), and enhancing social behaviour and cognition in VPA-exposed offspring (Prince et al., 2024) .

Key neurobiological pathways involved in neuropsychiatric conditions were also altered by prebiotics, including corticosterone levels and BDNF expression in the hippocampus. Nonetheless, prebiotics and their effects on mental health are still under investigation and the research needs to be conducted in humans to grasp the full therapeutic potential of prebiotics

- *FMT (Fecal Microbiota Transplantation)*

FMT is conducted by the application of the therapeutic population of the microbes. FMT is an attractive technique to substitute the pathogenic microbes with the healthy microbes. It entails relocation of healthy microorganisms to the recipient of healthy donors using different delivery methods. The donor should be screened on stringent guidelines (Cammarota et al., 2017). To ensure that the donor infects the recipient, it is required that appropriate stool and blood tests be conducted within 4 weeks prior to transplantation (Cammarota et al., 2017). To the induce immunotolerance by the recipient to the microbes of the donor, it is preferable that a close relative of recipient is used as the donor (Bakken et al., 2011) and not an unrelated donor in the event of a genetic disease like inflammatory bowel disease (Kelly et al., 2015). It was discovered that fecal filtrate with bacterial debris, metabolites, DNA etc. was simply sufficient to treat recurrent Clostridioides difficile infection (CDI) (Ott et al., 2017; Zuo et al., 2018). Recurrent CDI was treated with pure culture of intestinal bacteria of one healthy donor only (Petrof et al., 2013). FMT has been effectively employed in the treatment of antibiotic caused dysbiosis in C. difficile infection (Quraishi et al., 2017; van Nood et al., 2013). FMT has also been effectively applied in treating recurrent C. difficile infections with a breathtaking percentage of recovery (Baktash et al., 2018) (with the percentage of success significantly lower than those of CDI) (Allegretti et al., 2019). The fecal microbes of the lean mice had to be transferred to the obese mice to restore the butyrate producing bacteria and enhance the production of insulin (Vrieze et al., 2012). Post FMT, the prevalence of antibiotic-resistant pathogens linked to infections of the urinary-tract were radically decreased (Tariq et al., 2017). Some diseases like alcoholic hepatitis and cirrhosis are linked with the lack of the mucosa-associated invariant T-cells. FTM has been found to restore these T-cells in patients (Gao et al., 2018). Likewise, the loss of Bacteroidetes caused by alcohol was recreated following FMT (Ferrere et al., 2017). Successful efficacy Experts related to FMT have carried out a number of clinical trials in the case of liver disorders, evolution of fibrosis, hepatic encephalopathy and alcoholic hepatitis ("Home | ClinicalTrials.gov," n.d.) FMT has been effectively researched in some neurological disorders like autism, sclerosis and Parkinson disease (Finegold et al., 2002). The fecal microbes transfer of healthy to cancer patients enhanced the response to the immune checkpoint inhibitors (Sweis et al., 2016). The effectiveness of the FMT methodology is determined by whether or not the microbes that are transferred is hereditary based on the host genes associated with the immune system (Hall et al., 2017). FMT has been found to be effective in ulcerative colitis treatment with the probability of remission (Paramsothy et al., 2019; Rossen et al., 2015). In the same manner, the FMT therapy did not prove useful in chronic Crohn disease (Sokol et al., 2020). The immunocompromised individuals are likely to experience adverse effects of fecal transfer as in the case of the transfer of β-lactam-resistant Escherichia coli. The negative impacts of FMT and the danger presented by the bad stools (Kump et al., 2018) compelled a different method of FMT in the shape of the artificial stool wherein commensals of stool could be fermented and formulated in vitro in the conditions akin to the ones of the human gut and subsequently packaged in the living form (Petrof and Khoruts, 2014). Also, the stool of the patient may be replaced to reinstate the original gut microbes in case of intense infections.

VI. CONCLUSION

The gut microbiome is essential for human health, interacting dynamically with the central nervous system through the gut-brain axis. This intricate two-way communication system combines neural, endocrine, immune, and metabolic pathways, emphasizing the microbiome's role as a crucial controller of physiological and neurological processes. Microbial metabolites, including short-chain fatty acids and tryptophan derivatives, have a significant impact on brain function, immunity, and behavior. Dysbiosis is strongly linked to neurodegenerative and neurodevelopmental conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and autism spectrum disorder. Progress in multi-omics technologies and sequencing techniques, especially 16S rRNA and metagenomics, has improved our knowledge of microbial diversity and function. Emerging treatment approaches,

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including probiotics, prebiotics, and fecal microbiota transplantation, present promising opportunities for influencing the microbiome. However, additional human studies are necessary to confirm these interventions and fully realize their clinical potential.

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