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REVIEW PAPER

Gut-brain axis: a critical review of its influence on neurological disorders

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ABSTRACT

The gut-brain axis is a well-known entity that is important in maintaining homeostasis. In the last decade, we have seen the importance of the microbiota as one of the critical regulators of brain function, and this has led to the appreciation of the importance of a distinct microbiota-gut-brain axis. This axis is under research for various biological and physiological bases of psychiatric, neurodevelopmental, age-related, and neurodegenerative disorders. The microbiota and the brain communicate via various routes, including the vagus nerve, immune system, tryptophan metabolism, and the entero-endocrinal system through the production of various microbial metabolites. Many factors can influence microbiota composition in early life, including infection in utero, mode of delivery, use of antibiotic medications, the nature of nutritional provision, environmental stressors, and genetic composition. Various research is ongoing regarding the role of microbiota in many conditions, including autism, anxiety, obesity, schizophrenia, Parkinson's disease, and Alzheimer's disease. In this article, we attempt to briefly elucidate the gut microbiota, its composition, its importance in the gut-brain axis, its associated pathways, and the diseases caused by microbiota dysbiosis.

***Keywords:** Gut microbiota; gut-brain axis; ENS; psychobiotics; faecal microbiota transplantation.*

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INTRODUCTION

Over 2000 years ago, Hippocrates is believed to have asserted that the origin of all diseases lies within the digestive system.[1] In recent times, there has been a surge in scientific investigations into the microbial communities residing in the intestines and the connection known as the Gut-Brain axis. This axis denotes a two-way channel of communication connecting the central nervous system (CNS) and the enteric nervous system (ENS), establishing a link between the brain's emotional and cognitive centres and the peripheral functions of the intestines. The Gut-Brain axis is significantly influenced by the gut microbiota, a multitude of bacteria and microorganisms inhabiting various parts of the human body, such as the skin, mouth, sexual organs, and intestines. These symbiotic organisms are crucial for maintaining the body's internal balance and may also contribute to the development of various metabolic, immune, and neurological disorders. The intricate interplay between the microbiota and the brain involves a sophisticated network of neural, endocrine, immune, and humoral elements[2]. In clinical

settings, evidence supporting the interaction between the microbiota and the brain emerges from observations linking gut dysbiosis to central nervous disorders like autism, anxiety-depressive disorders, and functional gastrointestinal disorders such as irritable bowel syndrome (IBS).[2]

Gut Microbiota

The gut microbiota represents an intricate community of bacteria coexisting in symbiosis, crucial for maintaining ecological equilibrium. An estimated 100 trillion bacteria inhabit an adult's body, with 80% residing in the gut, surpassing the combined count of human cells tenfold. Hosting over 100 bacterial species, the gut microbiome is primarily shaped by two bacterial phylotypes: Bacteroidetes and Firmicutes. Additionally, smaller proportions of Proteobacteria, Actinomyces, Fusobacterium, and Verrucomicrobia contribute to this diverse environment alongside viruses, protozoa, archaea, and fungi.[3]

The gut microbiota composition is dynamic, evolving with human development and influenced by various stressors. Neonates inherit their initial microbiome from their mothers, gradually forming a complex gut microbiome resembling that of adults by the age of one. Throughout life, gut microbiota composition remains fluid, subject to alterations influenced by age, infection, drugs, illnesses, and diet. Notably, stress in the early years may induce microbiota changes, presenting a potential risk factor for stress-related disorders in adulthood.[3]

The functions of gut microbiota are multifaceted. Primarily, it forms the intestinal barrier, supporting gut microbiota's sustained presence, fostering intestinal epithelial cells' regeneration, and generating mucus. Additionally, it nourishes the mucosa by producing short-chain fatty acids (SCFAs).[3] Gut microbiota actively participates in the maturation of the immune system, stimulating the innate immune system during early life and contributing to the development of intestinal-related lymphoid tissue. It further inspires acquired immunity by eliciting local and systemic immune responses. The microbiota is instrumental in synthesizing and metabolizing certain nutrients, hormones, and vitamins in the intestines. Moreover, it plays a crucial role in removing drugs and toxins from the body. Under physiological conditions, gut microbiota perpetuates the stimulation of the immune system, resulting in a state of "low-grade physiological inflammation," a swift and effective mechanism for defending against pathogens.[3]

The Gut-Brain Axis

The precise communication mechanism between the gut microbiota and the brain remains incompletely comprehended. The influence of the gut microbiota on the brain extends beyond the neuroanatomical pathway of the enteric nervous system, involving interactions with the endocrine, immune, and metabolic systems.[4] This bidirectional communication, recognized as the gut-brain axis, characterizes the dynamic relationship between the gut and the brain. Additionally, the interplay between the gut microbiota and the gut-brain axis is often denoted as the gut microbiota-gut-brain axis.[5]

Within the realm of gut-brain signalling, four principal pathways play a pivotal role—namely, the neural pathway, enteroendocrine signalling, serotonin and tryptophan pathway, and immune signalling. These pathways, elucidated below, contribute to the intricate network through which the gut and brain communicate.[6,7]

Neuroanatomical pathways

The gut and the brain communicate through two pathways. One involves a direct information exchange between the gut and the brain through the autonomic nervous system (ANS) and the Vagus nerve (VN). The other pathway is a bidirectional communication between the enteric nervous system (ENS) in the gut and the ANS and Vagus nerve in the spinal cord. The control of gut functions is

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organized into four levels: the ENS, prevertebral ganglia, ANS in the spinal cord, and brainstem nuclei.[8]

The brainstem nuclei regulate various gut functions. Afferent fibers of the Vagus nerve stop at the brainstem nucleus tractus solitarius and then project upward to the thalamus, limbic lobe, and insular cortex. Spinal afferent fibers also ascend to the thalamus and medulla oblongata. Thalamic fibers project to the sensorimotor areas and insular cortex. Damage or abnormalities at these levels can affect intestinal function regulation, including local intestinal reflexes.[3]

Direct communication between gut microbiota and the brain occurs mainly through the Vagus nerve. Bacteria stimulate afferent neurons of the ENS, and signals from the gut can trigger anti-inflammatory responses, protecting against microorganism-induced septicemia. The Vagus nerve transmits signals from specific gut bacteria, such as Lactobacillus rhamnosus, influencing central gamma-aminobutyric acid (GABA) receptor expression and reducing anxiety and depressive behaviour. Bifidobacterium longum exhibits an anxiolytic effect in a colitis model through an intact Vagus nerve. Recent research suggests that many effects of gut microbiota or potential probiotics on brain functions depend not solely on Vagus nerve activation. Bacteria residing in the gut play a critical role in an individual's postnatal development, immune system maturation, and endocrine system. Newer pathways beyond Vagus nerve activation have been identified in these processes.[8]

Neuroendo crine hypothalamic-pituitary-adrenal axis

The gut microbiota plays a crucial role in the development of the neuroendocrine system. The absence of gut microbiota and the lack of toll-like receptor (TLR) expression contribute to a diminished neuroendocrine response to pathogens in the gut. For instance, mice lacking TLR4 had a reduced response to lipopolysaccharide (LPS) produced by Gram-negative bacteria. The Griseofulvin (GF) mouse model helps study the hypothalamic-pituitary-adrenal (HPA) axis regulated by microorganisms. The stress response in GF mice could be partially reversed by faecal microbial transplant and completely reversed over time by a single strain of Bifidobacterium infantis, highlighting the importance of gut microbiota in stress development.[9]

Research indicates that gut microbiota can influence neural circuits and behaviour related to the stress response. Changes in the hippocampal NMDA and 5-HT1A receptors in mouse models can impact the release and expression of corticotropin-releasing hormone in the hypothalamus, thereby altering HPA function. Early stress and maternal separation can lead to long-term changes in HPA and microbiome composition. Mice exposed to long-term restraint stress showed significantly different microbiome compositions than non-stressed mice.[9]

Repeated stress has been observed to decrease the quantity of Bacteroides in the cecum and increase the number of Clostridium. Stress also elevates levels of interleukin-6 and monocyte chemotactic protein-1 (MCP-1) in the blood, with MCP-1 being significantly associated with changes in stress-induced bacteria like Enterococcus faecalis, Pseudobutyrivibrio, and aerogenic bacteria Dorea strain.[9]

Bacterial byproducts interacting with the gut epithelium stimulate enteroendocrine cells to release neuropeptides. These peptides have local effects on the intrinsic enteric nervous system (ENS) and can enter the bloodstream to act on the central nervous system (CNS). Key neuropeptides involved in enteroendocrine signalling include peptide YY (PYY), neuropeptide Y (NPY), glucagon-like peptide (GLP-1 and GLP-2), and substance P.[9]

Gut immune system

The development of the gut immune system relies on gut microbiota. For instance, the segmented filamentous bacterium in the gut contributes to the full functionality of gut B and T lymphocytes. Bacteria engage with the

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host through various methods, with the host cell receptors called Toll-like receptors (TLRs) playing a crucial role in this communication. The human innate immune system has ten types of TLRs identified as pattern recognition receptors. These receptors, integral to the innate immune system, initiate the production of cytokine responses and are also widely distributed in the neurons. Consequently, neurons respond to both bacterial and viral components.[10]

Intestinal epithelial cells can transport microbial composition or metabolites into the inner environment, and the nervous system interacts with these bacterial and viral components. The balance of gut microbiota can influence the regulation of inflammatory responses, and this mechanism also plays a significant role in regulating emotions and behaviors.[11]

Neurotransmitters and neural regulators synthesized by intestinal bacteria

Serotonin (5-HT) is a crucial neurotransmitter in the brain and the Enteric Nervous System (ENS). Approximately 95% of 5-HT in the body is produced by enterochromaffin cells in the gut mucosa and neurons in the ENS. In peripheral functions, 5-HT regulates gastrointestinal secretion, motility (including smooth muscle contraction and relaxation), and pain perception. Within the brain, 5-HT signalling pathways regulate mood and cognition. Notably, spore-forming bacteria in the gut contribute to 5-HT biosynthesis from colonic enterochromaffin cells and are linked to gastrointestinal disorders (such as Inflammatory Bowel Disease) and mood disorders like depression.[3]

Gut bacteria also synthesize gamma-aminobutyric acid, butyric acid, dopamine, and Short-Chain Fatty Acids (SCFAs). These substances can freely exchange between microorganism cells, with intestinal cells in the gut producing numerous 5-HT molecules that impact the brain. Additionally, bacterial enzymes can generate neurotoxin products such as D-lactic acid and ammonia. Consequently, the gut microbiota plays a crucial role in generating several essential neurotransmitters in the body, influencing the brain and various aspects of human physiology, wherein many of these neurotransmitters are vital molecules in the human gut microbiota.[3]

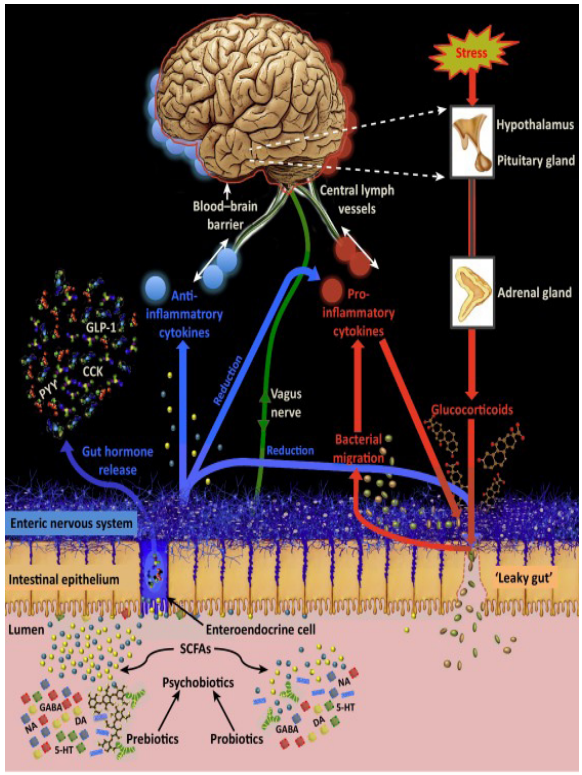

Figure 1 Systems-Level Overview of Psychobiotic Action. Blue arrows indicate psychobiotic processes and effects, while red arrows indicate leaky gut and inflammation processes. Pro-inflammatory cytokines (red circles) also reduce the integrity of the gut barrier. Psychobiotic action restores gut barrier function and decreases circulating concentrations of glucocorticoids and pro-inflammatory cytokines. They also increase concentrations of anti-inflammatory cytokines (blue circles), enhancing the integrity of the blood-brain and gut barriers and reducing overall inflammation[12]

Intestinal mucosal barrier and blood-brain barrier (barrier system)

In rodent studies, evidence indicates that stress alters the function of the intestinal

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mucosal barrier, allowing substances like LPS and other cytokines to enter the bloodstream. This, in turn, activates TLR4 and other Toll-like receptors, leading to the production of inflammatory cytokines. The inflammation produced peripherally can potentially increase the permeability of the blood-brain barrier. This heightened permeability allows inflammatory factors to impact the brain directly. Numerous studies involving both animals and humans have provided substantial evidence supporting the crucial role of gut microbiota in the development and functioning of the brain.[3]

Role of gut-brain axis in health

Bacterial colonization of the gut is central to the development and maturation of both ENS and CNS. The absence of microbial colonization results in altered gene expression and neurotransmitter turnover in the CNS and ENS. It also causes alterations in gut sensory-motor functions and delayed gastric emptying and intestinal transit. Lactobacilli generate nitric oxide and hydrogen sulphide that modulate gut motility by interacting with vanilloid receptors in the gut mucosa[13]. Microbiota influences stress reactivity and anxiety-like behaviour by regulating the hypothalamic-pituitary axis (HPA) set point.[14] They also modulate the serotonergic pathways in the limbic system. The microbiome influences gut motility by maintaining the mucous layer and biofilm through the secretion of various acids, bicarbonates, and mucus. This helps in intestinal fluid handling and mucosal immune responses.[15,16]

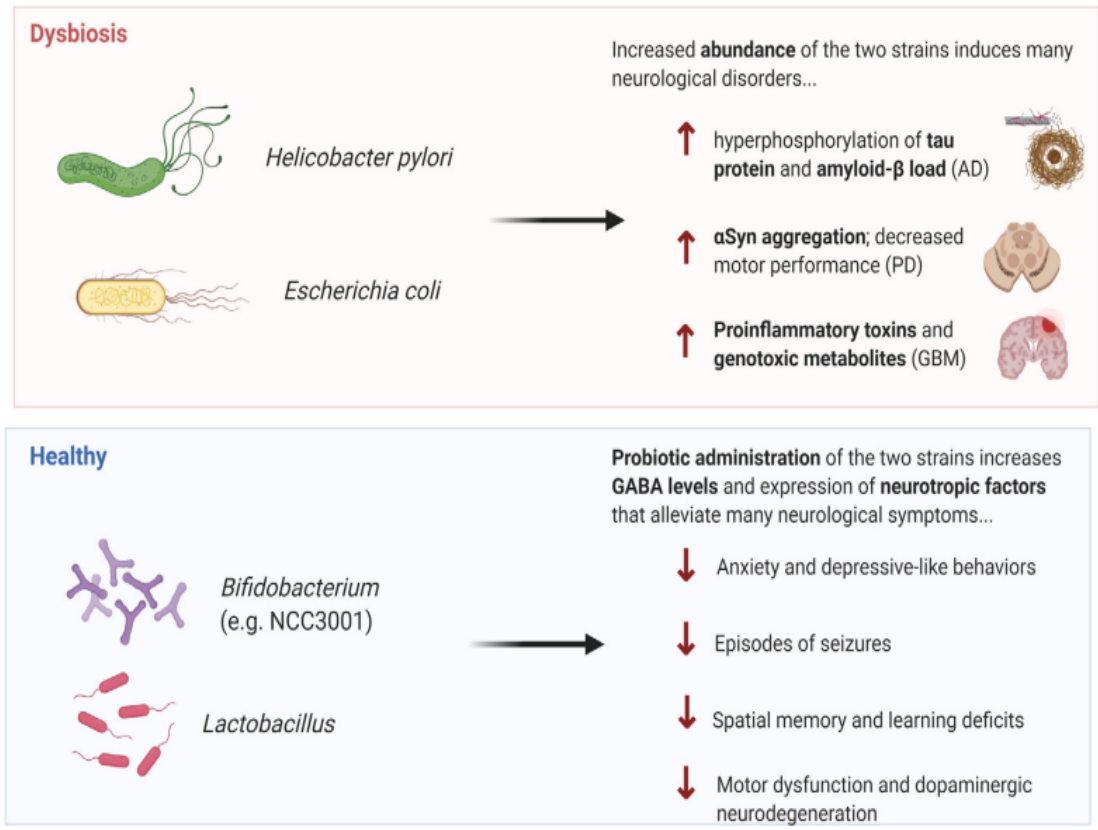

Figure 2 Microbial modulate the development and treatment of CNS disorders[17]

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Role of the gut-brain axis in disease

The role of microbiota in disease was noticed several years back when gut antibiotics were given for hepatic encephalopathy. The role of microbiota is rapidly emerging in gut-brain communication, and alterations in the composition of gut microbiota have been observed in several diseases.

Depression

Patients experiencing depression show significant changes in the composition of their gut microbiota, particularly in Acinetobacter and Bacteroides. When mice were exposed to microbiota from depressed patients, they exhibited depressive behaviour and disruptions in hippocampal gene activation. Depression in individuals is linked to abnormalities in both the immune system and the brain, leading to reduced levels of 5-HT and brain-derived neurotrophic factor, as well as alterations in neuronal morphology within the amygdala. Key products of the gut microbiota, such as short-chain fatty acids (e.g., butyrate, propionate, and acetate), play a crucial role. The heightened production of acetate by the modified gut microbiota triggers the activation of the parasympathetic nervous system, resulting in increased glucose-stimulated insulin and ghrelin secretion. This cascade effect contributes to hyperphagia, obesity, and other related outcomes associated with depression.[18]

Irritable Bowel Syndrome

Changes in the gut microbiota lead to abnormalities in the HPA axis, increasing the synthesis of corticotropin-releasing hormone (CRH), a factor linked to irritable bowel syndrome (IBS). CRH notably impacts gut motility and sensitivity, contributing to diarrhoea. Dysfunction in the autonomic nervous system (ANS), coupled with impaired parasympathetic function, leads to alternating patterns of diarrhoea and constipation, influenced significantly by social stressors.[19] An altered gut-brain axis (GBA) is connected to low-grade inflammation or immune activation in the gut, bringing about changes in intestinal motility and sensations. Functional MRI studies illustrate heightened metabolic activity in specific brain regions, such as the anterior cingulate, prefrontal cortex, and insula, in individuals with IBS. These areas are closely tied to the intricate network of the gut-brain axis.[20]

Autism Spectrum Disorders

This neurodevelopmental disorder is characterized by challenges in social interaction and communication skills, accompanied by restricted activities, repetitive behaviours, and varying degrees of intellectual disability. Gastrointestinal (GI) symptoms and feeding difficulties are prevalent, typically aligning with the severity of autism spectrum disorder (ASD).[21] In addition to genetic and environmental factors, altered gut microbiota and oxidative stress are implicated among the various etiologies. Studies have linked increased levels of Ruminococcus and Bacteroides and decreased levels of firmicutes to ASD. Stool samples from children with ASD reveal diminished short-chain fatty acids (SCFA), including acetic acid, propionic acid, and butyric acid, indicating disruptions in gut microbiota. Certain bacteria, such as Clostridium tetani and Desulfovibrio, have been directly associated with exacerbating autism. Interventions like probiotics and gluten-free diets have been shown to modulate gut microbiota composition and enhance the intestinal immune system, leading to improved symptom control in children with ASD.[2]

Parkinson's disease (PD)

Parkinson's disease is a well-studied example where the initiation of PD aetiology is suspected to begin in the intestines. There is emerging evidence of deposition of alpha-synucleins in the Enteric nervous system as early as a few years to decades before the symptom onset in Parkinson's disease. This explains the reason why almost 80% of individuals with PD experience constipation issues that often precede PD diagnoses by several years.[22]

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Furthermore, some gut bacteria have even been associated as highly sensitive biomarkers for PD diagnosis, such as Prevotellaceae, which was found to sharply decline following PD onset, and Enterobacteriaceae, whose increased abundance was found to correlate with PD symptom severity positively. Remarkably, a recent model for diagnosing PD is being utilized by the Prevotellaceae abundance and constipation status, which shows a specificity of 90.3%.[23]

Alzheimer's disease (AD)

Alzheimer's disease (AD) aetiology has also been strongly linked to the altercation of gut microbiota; metabolic molecules from microbiota have been associated with phosphorylated tau proteins and Amyloid beta peptide 42 biomarkers and activation of the NLRP3 inflammasome pathway.[24] The buildup of amyloid peptide deposition catalyzes the release of various pro-inflammatory molecules that cause neuroinflammation in Alzheimer's disease pathology.[25] H. pylori bacteria have been reported to induce hyperphosphorylation of tau protein and secretion of inflammatory mediators and amyloid proteins, which subsided after treating H. pylori infection via triple eradication therapy. This phenomenon was also surprisingly associated with decreased cognitive decline in a few patients with Alzheimer's disease.[24]

Multiple sclerosis (MS)

Multiple sclerosis, although not as extensively studied concerning associations with the gut microbiome, requires some discussion. A clinical trial investigation of gut microbial profile in MS patients has revealed elevated levels of specific microbial taxa, including Akkermansia muciniphila and Acinetobacter calcoaceticus, that were later found to be associated with increased pro-inflammatory T-cell response and weakened T regulatory cell activity in few in-vitro studies. Such findings have been reproduced in a few other studies, which include a link between increased levels of Fusobacteria and the future possibility of MS relapse.[26] Few studies in mice, where faecal microbiota transplantation (FMT) from MS patients showed the development of experimental autoimmune encephalomyelitis (EAE) compared to fewer anti-inflammatory regulatory T-cells in mice that received FMT from healthy individuals.[26]

Future therapeutic directions

There are two main strategies for manipulating gut microbiota. One is a targeted approach that defines the offending microorganism and eliminates it directly or by inducing an immune response to it through vaccination. The second approach involves manipulating the whole microbiome with antibiotics, probiotics, prebiotics, or faecal microbiota transplants. Another novel therapeutic approach includes bacteriophage therapy, targeting bacterial genes to modify the microbiome suitably. However, there are some unexpected side effects with these therapies, like peripheral neuropathy in some cases given FMT and accelerated atherosclerosis in experimental mice undergoing manipulation of the brain axis. Therefore, more long-term safety data is needed in this promising field of medicine.

Psychobiotics

Psychobiotics refer to a class of probiotics (live bacteria and yeast) that positively influence mental health and well-being when ingested in adequate amounts. The term is derived from the combination of "psycho," relating to the mind, and "biotics," referring to living organisms. This emerging field explores the intricate connection between the gut and the brain, emphasizing the bidirectional communication system known as the gut-brain axis.[27]

Psychobiotics aim to positively impact mental health by promoting a balanced and healthy gut microbiome. Several strains of bacteria, such as Lactobacillus and Bifidobacterium, are commonly associated with psychobiotic effects. These microorganisms are believed to produce neurotransmitters, modulate inflammation, and influence the

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production of short-chain fatty acids, all of which can profoundly affect the brain.[27]

Studies have demonstrated the potential of psychobiotics in alleviating symptoms of conditions like anxiety, depression, and even neurodevelopmental disorders. While the field is still in its early stages, and more research is needed to fully understand the mechanisms and optimal strains for specific mental health benefits, psychobiotics offer a promising avenue for novel mental health and well-being interventions.[27]

Fecal microbiota transplant

Faecal Microbiota Transplantation (FMT) is a medical procedure in which faecal matter, typically from a healthy donor, is transferred into a patient's gastrointestinal tract to restore or improve the balance of the gut microbiota. The procedure is also known as faecal bacteriotherapy or faecal transplant. Disruptions in the balance of the gut microbiota, often due to factors like antibiotic use, infections, or chronic diseases, can lead to gastrointestinal issues and other neurological health problems.

FMT primarily treats recurrent Clostridium difficile infection (CDI), a severe and persistent bacterial infection that causes diarrhoea and can be challenging to manage with standard antibiotics. By introducing a healthy donor's faecal material into the patient's colon, FMT aims to replenish the gut microbiota with beneficial bacteria, suppressing the overgrowth of harmful bacteria like C. difficile.[28]

The procedure is typically performed through various methods, such as colonoscopy, nasogastric or nasoenteric tube delivery, or capsules containing freeze-dried faecal material. While FMT has shown remarkable success in treating recurrent clostridium difficile infection, research is ongoing to explore its potential applications for other conditions, including inflammatory bowel disease, irritable bowel syndrome, autism spectrum disorders and even neurodegenerative disorders.[28]

CONCLUSION

Current literature and research suggest that the gut microbiota is essential in maintaining a healthy Gut-Brain axis. It interacts with the CNS by regulating brain chemistry and influencing neuroendocrine systems associated with stress response, anxiety, and memory function. Chronic stress and overuse of antibiotics alter the microbiota composition and function and can result in various neuropsychiatric diseases. Judicious use of antibiotics and a healthy lifestyle with a predominantly plant-based diet shall go a long way in helping the Gut-Brain axis. Controlled manipulation and alterations in the gut microbiome is a promising new area of research that may give solutions to some chronic functional disorders like IBS, Anxiety, Autism spectrum disorders, ADHD and CNS inflammatory disorders like Multiple sclerosis and neurodegenerative conditions like Parkinson's disease and dementia.

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