IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

PROBIOTIC POTENTIAL: EXPLORING THE GUT-BRAIN-AXIS IN CENTRAL NERVOUS SYSTEM DISORDER

[1]Vaishnavi Suraj Patil, [2]Siddhi Vivek. Khare, [3]Jeevisha Sandip Satpute, [4]Divya Gulab Chandra Maurya

[5]Krutika Arun More,

[1]Student, [2]Student, [3]Student, [4]Student, [5]Assistant Proffesor.

[1]Doctor of Pharmacy, [2]Doctor of Pharmacy, [3]Doctor of Pharmacy, [4]Doctor of Pharmacy, [5] Pharmaceutical Chemistry
Mahatma Gandhi Vidyamandir Pharmacy College, Nashik, India,

Abstract; Probiotics are described as live microorganisms that benefit the host by enhancing its intestinal microbial composition. Studies have suggested a possible link between the digestive system and mental health. The moniker "Gut-Brain Axis" has been applied to this link.

Probiotics known as "psych-biotics" work with commensal gut bacteria to provide mental health advantages to the host when consumed in specific amounts.

According to the study, the bacteria found in probiotics stimulate the immune system or enteric nervous system by

1) Acting on the hypothalamus-pituitary axis,
2) Directly affecting the immune system, and
3) Secreting neurotransmitters.

The brain may also modify intestinal permeability, which permits probiotic bacteria to pass through the epithelium and trigger an immune response in the mucosa, influencing the makeup and function of the microbiota. They can be applied to several neurological conditions, including autism, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and Huntington's disease.

The degenerative mechanisms of neurons, which are triggered by a variety of cytotoxic chemicals such as cytokines, exotoxins, reactive oxygen species, and many more, resulting in a variety of neurological diseases or disorders.

The primary cause of these inflammatory mediators is an imbalance in the gut flora. Probiotic administration aids in their balance and produces short-chain fatty acids, propionates, and butyrates—all of which are created when non-digestible carbohydrates are fermented by bacteria.

These substances are recognized to have beneficial effects on neurological health, and sufficient clinical data from researchers has been presented; this has been covered in the subsequent review article.

Index Terms - Probiotics, Psych-biotics, Gut-Brain – Axis, Neurodegenerative diseases, Microbiota.

INTRODUCTION

Metchnikoff first used the term "probiotic" in 1908; it is a combination of the Greek term's "pro" and "bios," which means "for life." Probiotics are described as live microbial supplements that improve the intestinal microbial composition of the host, hence exerting a favorable influence on it. "Mono or mixed strains of living microorganisms which confer desirable health benefits on the host when used adequately" is the more recent definition that FAO/WHO accepted in 2002. A bacteria must be nonpathogenic, able to produce a viable cell count, beneficial to the host's health, and able to improve intestinal tract functioning to be classified as a probiotic. About 200 years ago, scientists hypothesized a relationship between mental health and GIT.[1]

The brain, spinal cord, ANS, ENS, and the hypothalamic-pituitary-adrenal (HPA) axis are the components of the brain-gut axis.[2]

Mechanism of Action

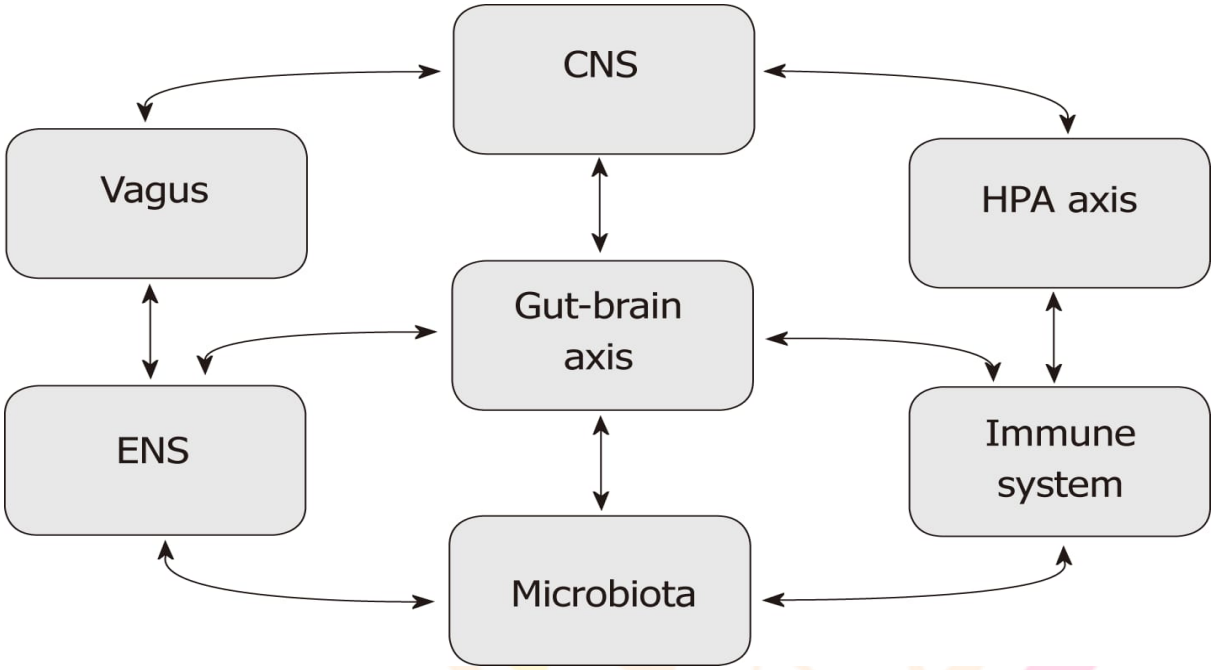

figure 01 : [3]

It has been discovered that these bacteria work by stimulating the immune system or the enteric nervous system.
There are three ways in which this can occur:
Firstly, through modulating the stress response of the hypothalamic-pituitary-adrenal (HPA) axis and diminishing systemic inflammation.
Secondly, through an immediate impact on the immune system.
Thirdly, through the release of chemicals like proteins, neurotransmitters, and short fatty acid chains.[4]
Probiotic supplementation affects the host gut microbiota through competition (for nutrients and adhesion to the intestinal epithelium), antagonism, and cross-feeding, among other mechanisms that are thought to mediate the therapeutic and prophylactic effects of probiotic administration.
Probiotics have been shown to affect innate and adaptive (cell-mediated and humoral) immunity, among other host immune functions. Additionally, probiotics improve immunity against pathogens by upregulating antibody secretion and phagocytosis. They also upregulate pro-inflammatory cytokines and various anti-inflammatory factors, which may lessen intestinal inflammation.
By reducing inflammation, probiotic strains also enhance the function of the gut barrier. Neuroactive compounds (or precursors) derived from microbes include acetylcholine, noradrenaline, oxytocin, serotonin, tryptophan, tryptamine, and gamma-aminobutyric acid (GABA). Probiotics play a crucial role in mitigating the symptoms of lactose maldigestion by enhancing lactose digestion within the host digestive system through the production of enzymes such as β-galactosidase and bile salt hydrolase.
The gut-brain axis (GBA), which connects the brain's emotional and cognitive centers to peripheral intestinal functions, is a bidirectional communication channel between the central and enteric nervous systems. Through signaling from the gut microbiota to the brain and from the brain to the gut microbiota via neural, endocrine, immune, and humoral links, this interaction between microbiota and GBA appears to be bidirectional.
Through controlling brain chemistry and affecting neuro-endocrine systems linked to stress response, anxiety, and memory function, the interaction with the central nervous system is accomplished. Numerous of these effects seem to be strain-specific, indicating that some probiotic strains may play a new role in adjuvant therapy for neurologic disorders.
Psychological stressors vary in their ability to modify the enteric microbiota's composition and total biomass, regardless of their duration. These effects may be mediated both directly through host-enteric microbiota signaling and indirectly through alterations in the intestinal milieu through the parallel neuroendocrine output efferent systems (autonomic nervous system and HPA). The so-called "emotional motor system" is made up of these efferent neural pathways that are connected to the endogenous pain-modulator pathways.
The brain might also affect microbiota composition and function by altering intestinal permeability, allowing bacterial antigens to penetrate the epithelium and stimulate an immune response in the mucosa.
The presence of neurotransmitter receptors in bacteria is necessary for communication between CNS effectors and bacteria. Bacteria contain binding sites for enteric neurotransmitters that the host produces. These binding sites can affect the function of various microbiota components, increasing susceptibility to inflammatory and infectious stimuli. To maintain the mucus layer and biofilm, where individual groups of bacteria grow in a variety of distinct microhabitats and metabolic niches associated with the mucosa, the brain plays a significant role in modulating gut functions, such as motility, secretion of acid, bicarbonates, and mucus, intestinal fluid handling, and mucosal immune response.[5]

USE OF PSYCHO-PROBIOTICS IN CENTRAL NERVOUS SYSTEM

1. MULTIPLE SCLEROSIS (MS)

- **What is Multiple Sclerosis?**

The myelin sheaths protecting nerve cells in the brain and spinal cord are damaged in multiple sclerosis, an inflammatory disease. Immune-mediated demyelination of neuronal axons is indicative of multiple sclerosis; aberrant CD4+ T-cells are the source of the immune response. The assault on the myelin sheath starts when hyperreactive Th1 and Th17 cells release pro-inflammatory biomarkers like cytokines. This suggests that internal tissues are mistakenly attacked by the immune system, which is meant to combat external substances like bacteria and fight diseases. In MS, the myelin sheaths that encase the nerve fibers are attacked by the immune system.

This illness results in lesions, plaque, or sclerosis wounds that can harm or even completely remove myelin from the nerve field. The nervous system's inability to transfer messages properly is brought on by myelin sheet degeneration, which can result in messages being sent slowly or incorrectly. All neurologic warning signs and symptoms are present in an MS patient; autonomic, ocular, motor, and sensory nerves are the most commonly affected.[6]

- **Pathophysiology Of Multiple Sclerosis (MS)**

MS is characterized by low-grade inflammation and microglial activation at the plaque borders along with diffuse injury of the normal-appearing white matter outside the plaque. Diffuse gray and white matter atrophy predominates in the disease's progressive course. Secondary demyelination follows inflammatory responses, microglial activation, axonal damage, and myelin damage that occur during this course. Since MS is characterized by immune-mediated demyelination of neuronal axons, aberrant CD4+ T-cells are the source of the immune response. The assault on the myelin sheath is started by the overreactive Th1 and Th17 cells' release of pro-inflammatory biomarkers like cytokines. They displayed the necessary characteristics, including demyelination, astrocytic gliosis, preferential destruction of small-caliber axons, and oligodendrocyte loss.

The release of non-specific products by activated macrophages and microglia, such as cytotoxic cytokines, excitotoxins, reactive oxygen, or nitric oxide species, can especially harm myelin sheaths.[7]

The mucus layer, which is composed of mucins and anti-bacterial molecules, the epithelial cells that are connected by tight junction proteins, and a diverse population of cells involved in the interaction with microbes, including M cells, elongations of "antigen-presenting cells" that reside in the lamina propria, intraepithelial lymphocytes, and Paneth cells that secrete anti-bacterial peptides, are the components that make up the gut barrier. Intestinal permeability (IP) alterations in multiple sclerosis (MS) have been documented, and the impact of these alterations on organs distant from the gut has also been studied recently. The disruption of the microbiota that underlies the emergence of neuroinflammation in human diseases such as MS and animal models is a related topic. Gaining more insight into the mechanisms by which IP modifications contribute to the pathophysiology of neuroinflammation is now of interest.[8]

- **Role of probiotics in MS**

It is thought that the bacteria in your intestines, also known as your gut microbiome, are crucial to the health of your immune system. Researchers studying multiple sclerosis (MS) have discovered that the gut microbiomes of those who have the disease differ from those of healthy people. Furthermore, a connection has been discovered by researchers between the gut flora of MS patients and a higher frequency of TH17 cells, an immune system cell type that is crucial to the pathophysiology of MS. According to the gut bacteria/immune system link, the organisms that are growing in your stomach might have an impact on the activity of your MS disease.[9]

The intestinal barrier protects the integrity of the gastrointestinal tract using an intestinal mucosal body defense system breach and signifies the neuronal demyelination and has an impact on the central nervous system. The gut microbiota in an animal host can control body temperature and behavior through chemical communication, including "direct" and "indirect" signaling, with the nervous system. The byproducts of intestinal bacterial fermentation, butyrate, propionate, and acetate, are known as short-chain fatty acids (SCFAs) and are crucial for the regulation of intestinal adaptive immune responses and brain function.

In MS patients, bacteroid are found in lower concentrations in obese individuals than in people with normal weights. Iron deficiency anemia is also a common occurrence in MS patients, according to numerous studies. Thus, by decreasing oligodendrocyte-myelin cells, iron deficiency can slow down the myelination process. Probiotics have been shown by researchers to improve iron absorption and lessen MS-related problems.[10]

2. PARKINSON'S DISEASE (PD)

- **What is Parkinson's Disease?**

Parkinson's disease (PD) is a multisystemic disorder characterized by a wide range of nonmotor symptoms, such as gastrointestinal (GI), urogenital, neuropsychiatric, sleep, and pain/sensory disturbances, in addition to motor symptoms like tremors, stiffness, and balance issues (bradykinesia). Individuals suffering from Parkinson's disease (PD) exhibit significant gastrointestinal dysfunction and intestinal dysbiosis.[11]

- **Pathophysiology of Parkinson's Disease**

The two main pathological features of Parkinson's disease (PD) are the build-up of α-synuclein , which is also referred to as Lewy bodies and Lewy neurites, and cell death in the brain's basal ganglia. In the substantia nigra pars compacta, up to 70% of the dopamine-secreting neurons are affected by the end of life. This vagal nerve dysfunction and characteristic movement disorder linked to Parkinson's disease (PD) are caused by damage to dopaminergic neurons. Numerous neurodegenerative diseases are characterized by gliosis, and new research suggests that a key factor in the dopaminergic degeneration of Parkinson's disease (PD) is the persistent activation of microglia and astrocytes.
Between the contents of the intestinal lumen and the circulating blood, the intestinal epithelium forms a regulated barrier known as the intestinal epithelium barrier (IEB), which serves to absorb and secrete nutrients as well as block the entry of externally harmful pathogens. The epithelial tight junctions, which link neighboring enterocytes to control paracellular permeability through the lateral intercellular space, are the most significant structures within the IEB. These junctions are made up of high molecular weight proteins known as zona occludes, which connect transmembrane proteins like occluding and claudins to the actin cytoskeleton. The GM and its metabolites have an impact on these structures and are essential for the exchange of information between the gut and the brain.
Each of the previously discussed components of the gut-brain axis may be differently impacted to varying degrees by PD pathology.[12]

- **Roles of Probiotics in Parkinson's Disease**

According to available data, the unknown external pathogen that eventually causes Parkinson's disease (PD) enters the gastrointestinal tract, disrupting the gut microbiota before slowly penetrating the intestinal epithelial barrier and reaching the central nervous system (ENS). In Parkinson's disease, α-syn deposition may initiate in the ENS, build up to a specific level, and ultimately spread to the central nervous system through trans-synaptic cell-to-cell communication. A pro-inflammatory environment in the GI tract may also be brought on by the pathogen-induced GM translocation. These signals would be transmitted systemically by malfunctioning blood-brain barrier structures to a particular area of the brain. Research has revealed that α-syn can be found in the brain and the gut, indicating that the pathology of α-syn in Parkinson's disease may not start in the gut. As a result, we are still unable to definitively determine the digestive cause of PD. To establish a causal relationship between Gut Microbiota dysbiosis and Parkinson's disease (PD), more research on the GMBA and the effects of modifying the gut microbiota and microbial metabolites is required. While this field of study is still in its early stages, given that GM has been shown to modulate microglia and mediate neurophysiological processes on multiple levels, further research into the mechanism underlying Gut Microbiota influence and regulation of the CNS in Parkinson's disease (PD) may be conducted in the future.[13]

3. ALZHEIMER'S DISEASE(AD)

- **What is Alzheimer's Disease?**

A neurodegenerative condition that progresses over time is Alzheimer's disease (AD). It is characterized by severe impairments to motor, cognitive, and memory functions.[14]

- **Pathophysiology of Alzheimer's Disease**

Significant impairments in memory, cognition, and motor function are hallmarks of AD. This is primarily caused by beta-amyloid (Aβ) plaque deposition outside of the neuron or tau tangles within the neurons. This could eventually result in neuronal death through changes to calcium homeostasis, neuroinflammation, and vascular degeneration. Alzheimer's disease is closely linked to neuronal loss, synaptic dysfunction, and neuropil threads. The amyloid precursor protein (APP), an essential transmembrane in the protein processing pathway, is primarily linked to the pathophysiology of AD. One common pathology in AD is an accumulation of Aβ. Aβ is a peptide that is produced when APP is broken down by proteases. Through clathrinid-mediated endocytosis, APP is moved into the endosomal compartment from trans-Golgi networks. In the process, some APP is recycled by the endosome and returned to the cell surface. The non-amyloidogenic

pathway that controls APP on the cell surface involves the action of α-secretase, which functions at the N-terminal end of the Aβ domain. As a result, APP-α and membrane-tethered 83 amino acids with carboxy-terminal end (CTF) are formed. Therefore, γ-secretase will cleave CTF-83 further to form the intracellular domain of APP and P3 fragment. The amyloidogenic pathway will be entered by APP in the endosomal compartment.
In this pathway, the β-secretase interacts with the extracellular domain of APP to produce membrane-bound 99 amino acids that include APP-β and CTF-β (C99). To create the soluble Aβ fragment and APP intracellular domain, γ-secretase will subsequently cleave C99. When transition metal ions like ferrous and copper are present, the Aβ peptide oligomerizes and produces hydrogen peroxide enzyme. Lipid peroxidation will be boosted by this, leading to the final formation of 4-hydroxynonenal (4HNE). However, when glucose and glutamate transport is compromised, there is an increased calcium ion influx. This leads to the synthesis of inositol 1,4,5-trisphosphate (IP3), which in turn these calcium ions to be ejected from endoplasmic reticulum storage. Calcium-dependent calpain activation sets off cyclin-dependent kinase (CDK5), which in turn causes tau hyperphosphorylation. This leads to the formation of neurofibrillary tangles (NFTs), which in turn causes microtubule disintegration and axonal transportation impairment. Neuronal death results from this over time as a result of synaptic and neuronal dysfunction. Aβ plaques cause the release of cytokines like IL-1, IL-6, and TNF-α as well as chemokines like macrophage inflammatory protein-1 and IL8 from microglial cells. Microglial cells are activated by all of these, which in turn cause astrocytes to release cytokines, chemokines, and acute-phase proteins. One of the pathologies associated with AD is neuroinflammation, which is produced in the brain by activated astrocytes and microglia.[15]

- **Roles of Probiotics in Alzheimer's Disease**

The pathophysiology of AD is influenced by the gut microbiota through multiple pathways, including neuroinflammation, tau phosphorylation, Aβ abnormality, neurotransmitter dysregulation, and oxidative stress. These pathways are dysregulated as a result of a disruption in the composition of the microbiota and are linked to an increase in BBB permeability, which in turn causes neuroinflammation, the loss of neuronal cells, and eventually AD. Patients with AD show an increase in brain oxidation as the disease progresses. Reactive oxygen species (ROS) and the antioxidant system are two ways that the gut microbiota may affect the degree of oxidative state in AD.[15]

4. HUNTINGTON'S DISEASE (HD)

- **What is Huntington's disease?**

An inherited neurodegenerative condition called Huntington's disease results in progressive motor deterioration, cognitive impairment, and neuropsychiatric symptoms. Age-dependent penetrance of an extended sequence of cytosine–adenine–guanine (CAG) repeats in the huntingtin gene is the cause of Huntington's disease.[16]

- **Pathophysiology of Huntington's Disease**

The progressive loss of medium spiny neurons in the striatum is the pathology of HD. Patients with affected movements have abnormal chorea movements as a result of the loss of these glutamatergic neurons, which are part of the indirect movement control pathway that fine-tunes voluntary movements. Striatal neurons are dependent on layer 5 cortical motor neurons for a steady supply of BDNF. Wild-type huntingtin protein binds to exon II of the BDNF promoter via the transcriptional repressor REST in these motor neurons to stimulate BDNF transcription.
Dysbiosis, or changes in the composition of the gut microbiota, can have a deleterious impact on behavior, affective function, and cognition. It may also be linked to the advancement of certain diseases. The gut microbiota is a major modulator of communication between the brain and the gut. Moreover, a recent report linked Huntington's disease to gut dysbiosis
As a result, the BDNF promoter is activated, which increases BDNF transcription. Following its axonally transported passage via the corticostriatal pathway, the synthesized BDNF is released as a trophic factor onto the striatal neurons. The inability of the mutant huntingtin protein to stimulate BDNF transcription leads to a reduction in the amount of BDNF released at corticostriatal synapses in HD patients. Additionally, protein inclusion bodies obstruct BDNF's axonal transport to the intended synapse. Thus, the characteristic movement symptoms result from deprivation of BDNF and a progressive loss of the striatal neurons responsible for regulating voluntary movements.[17]

- **Roles of Probiotics in Huntington's Disease**

Human health depends on the gut microbiome's homeostasis, which affects behavior and brain function through the gut-brain axis. Therefore, through interactions between the gut, endocrine, immune, and neural pathways, some of the clinical signs or

alterations in the brain associated with Huntington's disease may be linked to gut-driven modulation of brain inflammatory pathways.[18]

5. AUTISM

- **What is Autism?**

In addition to deficits in social and cognitive skills, autism has been linked to gastrointestinal symptoms that are frequently reported in this population. They are distinguished by a certain level of difficulty in communication and social interaction. Atypical patterns of behavior and activity, such as trouble switching between activities, attention to detail, and peculiar responses to sensations, are additional traits.[19]

- **Pathophysiology of Autism**

Neuroanatomical research generally lends credence to the theory that autism could be caused by a combination of brain shrinkage in certain regions and enlargement in others. According to this research, aberrant neuronal growth and pruning during the early phases of fetal and postnatal brain development may be the cause of autism, leaving some regions of the brain with an excessive number of neurons and other regions with an insufficient number. While some studies have found that autism is associated with an overall enlargement of the brain, others have found abnormalities in the frontal lobe, limbic system, mirror neuron system, temporal lobe, and corpus callosum, among other brain regions.
The development factors that appear to cause autism affect many, if not all, functional brain development systems. These changes in the brain's structure include pathological overgrowth, though it is unclear whether this causes autistic symptoms.
There is evidence to suggest abnormalities of the gut-brain axis may be involved. According to a 2015 review, brain neuroinflammation and dysfunction may be brought on by immunological responses, gastrointestinal inflammation, autonomic nervous system dysfunction, changes in gut flora, and food metabolites. According to a review published in 2016, neurological conditions like autism may be influenced by anomalies in the enteric nervous system. Diseases that start in the intestines may be able to spread to the brain through neural connections and the immune system.
Important mechanisms include immune system disruption and heterochrony (disturbed neural migration or abnormal formation of synapses and dendritic spines). The mirror neuron system theory of autism postulates that distortion in the development of the MNS plays a major role in the various neurotransmitter abnormalities that have been found in autism, including a notable increase in serotonin levels in the blood. impairment of my ability to communicate and interact with others.[20]

- **Role of Probiotics in Autism**

Supplementing with probiotics can effectively prevent intestinal diseases and safeguard the intestinal barrier. Since probiotics' metabolic function may extend beyond their impact on colonial microflora, their role is no longer thought to be exclusively mediated by microflora. This allows for a greater variety of probiotic applications.
First metabolite lowers brain catecholamine levels, which can lead to autistic symptoms. Therefore, the lower concentrations of those metabolites may be what causes autistic children to have better eye contact and experience less constipation.[21]

Polyunsaturated fatty acids, particularly eicosapentaenoic acid, help treat depression and enhance the results of treating attention deficit or hyperactivity disorder. Probiotics and their byproducts have a significant potential therapeutic impact by regulating alterations in immune cells, cytokines, and emotional behavior. Therefore, to develop more potent treatments, it is imperative to conduct more thorough research on the pathophysiology of autism.[22]

FUTURE PERSPECTIVES OF PROBIOTIC UTILIZATION IN HEALTHCARE

By separating the complex networks of the immune system, gut microbiota, and microbiota-gut-brain axis, the field of microbiome evolution has made a major advancement toward our understanding of CNS disease treatments. In the future, it will be crucial to understand that the microbiome may play a significant role in the development, management, prevention, and treatment of CNS diseases. In this regard, even something as basic as a daily diet may have substantial therapeutic potential, particularly when combined with currently available treatments.
Furthermore, as our understanding of the gut microbiota grows, we will be able to develop new approaches for non-invasive prognosticators and predictive biomarkers (like fecal DNA sequencing to quantify community richness and the ratios of "beneficial" to "harmful" bacteria) for a range of CNS disorders and their corresponding outcomes. In the end, the microbiota's adaptability offers exciting possibilities and hope for opening up a new area for precision medicine.

CONCLUSION

Probiotics are dietary supplements that don't require a prescription. New research suggests that they may be able to help with several neurological conditions, including autism, multiple sclerosis, Alzheimer's, Parkinson's, and Huntington's diseases. The term "gut-brain axis" refers to the connection that has been shown through numerous studies between the central nervous system and the gastrointestinal tract.

The gut microbiota and the gut-brain axis appear to interact bidirectionally through signals from the gut microbiota and brain and vice versa via neuronal, endocrine, immune, and humoral activity. The gut-brain axis has bidirectional communication with the central and enteric nervous systems.

Probiotics are used in the demonstration of psycho-probiotics or pro-biotics which help modulate host immune function both innate and adaptive immunity. It increases phagocytosis and upregulates antibody secretion, they are responsible for various proinflammatory factors.

Further, the approach must be towards increasing the use of probiotics in prophylaxis and therapeutic uses in the treatment of various diseases. Not just the central nervous system but also it is used as a supplement that can be used in day-to-day life must be promoted so people can maintain a positive gut health which indirectly and directly helps in altering the entire body's well-being above disorder.

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