PSYCHOBIOTICS: THE NEXT GENERATION ADJUVANT THERAPY AND ITS REVOLUTIONARY CONTRIBUTION IN TREATMENT FOR PARKINSON'S DISEASE.

Abstract

Parkinson's Disease is a Neurodegenerative disorder. In prevalence Parkinson's Disease ranks second following Alzheimer's disease. Parkinson is not curable but treatment revolves around controlling the symptoms. Most preferrable approach is medicating with Levodopa drug, with time the drug dosage goes on increasing until reaches the highest level as gradually the drug keeps on decreasing its effectiveness besides it manifests multiple side effects within the patient's body. Doctors would last resort to surgery favourably deep brain stimulation that would reduce the drug dosage to certain level however effectiveness is only 30% to 60%. Substantial concern with the drug treatment is its conversion to dopamine within the gut itself before it reaches the brain and only 1 to 10% of dopamine gets available to the brain due this gut interference hence bioavailability of dopamine decreases and the doses keep on increasing unnecessarily. In order to overcome these concerns Psychobiotics serve as the most approachable adjuvant therapy. Psychobiotics are a set of probiotics that are used to treat neurodegenerative and neuronal disorders and nervous conditions. Psychobiotics exerts their effect directly by establishing in the gut and indirectly by sending signals via the gut-brain-axis. Particularly for Parkinson's disease it helps to lengthen the course of medication by preventing interference with drug treatment thus decreasing adaptability and controls the major side effects of the primary levodopa drug therapy used to treat Parkinson's disease. Overall increase the quality of life for Parkinson's patients especially for the ones with an early age disease onset.

Keywords: Parkinson's Disease, Psychobiotics, dysbiosis, gut-brain-axis, gut-interference

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I. INTRODUCTION

Psychobiotic therapy uses live bacteria taken as probiotic that establishes itself within the gut of the individual and works as desired. Psychiatrist Dr. Ted Dinan and neuroscientist Dr. John F. Cryan created the term "Psychobiotics."Psychobiotics exhibit anxiolytic and antidepressant effects characterised by modifications in neuronal, systemic, emotive, and cognitive indices. The enteric nervous system and the immune system interaction pathways that Psychobiotics affect upon. Your gut flora, or "psychobiome," has an impact on your behaviour and thought processes. Later, prebiotics, which promote the growth of good gut flora, were added to this definition to include them. Therefore, Psychobiotics are helpful bacteria (probiotics) or preparation for such bacteria (prebiotics) that influence the interplay between bacteria and the brain. Additionally, the term "Psychobiotics" should be used to refer to any exogenous factor whose impact on the brain is mediated by bacteria. Psychobiotics are a brand-new type of medication as a result of these discoveries. It is hoped that they will someday offer potent new treatments for depression and other mental health issues, as well as aid us in managing regular stress and worry. Psychobiotics can be taken orally as supplements in a variety of forms, including fermented foods like kefir and yoghurt, freeze-dried powder, and capsules [1].

II. GUT MICROBIOME

Human gut is a home to about 1013 to 1014 microorganisms, which is at least 10 times more than the number of human cells in our bodies and comprises of greater than 1000 species and above 7000 strains [2]. The beneficial bacteria are stored in the caecum, a pocket of the large intestine that is also related to the appendix. This way, if the good bacteria are completely eradicated by illnesses like diarrhoea, they can repopulate the digestive system.

Bacteria predominates however virus, archaea, protozoa and fungi also exists [3]. Most microorganisms cannot survive in the stomach due to its high acidity. Bacteria in the stomach include *Streptococcus*, *Staphylococcus*, *Lactobacillus*, and *Peptostreptococcus* [4]. In intestine Bacteroidetes and Firmicutes are present in higher amount as compared to *Proteobacteria, Actinobacteria, Fusobacteria*, and *Verrucomicrobia* phyla [5]. Microbial density in the colon exceeds that found in any other habitat on earth [6]. Up to 60% dry mass of fecal content is composed of these bacteria. Characterization of human microbiome was undertaken by two projects at large. HMP-Human microbiome project and Meta HIT-European metagenomics of the human intestinal tract. HMP was launched by US national institute of health (NIH) whereas Meta HIT was initiative by European commission and China. A few of useful outcomes of these projects were: 1) There was not a single taxon that was universally present in all individual but it kept on varying from person to person. 2) Variation as compared between two individuals was lower in a single individual indicating that microbiota stays stable with time. 3) Instability in microbiota is observed during illness. 4) 99.1%genes belonged to bacteria, 0.1% to virus and rest other eucaryotes. 5) Approx. 40% similarity was shared between microbiota of individuals. Currently other few projects are ongoing to study the human gut microbiome like NIH HMP 2, IHMC-International human microbiome consortium, MY NEW GUT program by European commission, MGP-Meta Geno Polis program, joint action intestinal microbiomics program [7]. Colonization of gut begins in infant at birth during delivery the infant is exposed to a complex microbiota mostly maternal and the establishment of microbiome occurs within three years after birth [8,9]. Complexity in

numbers and diversity of strict anaerobes increase by influence of diet and environment, and after a year adult-like microbiome starts to appear [10,11]. Gut microbiome play myriads of role within the host ecosystem that directly or indirectly helps the individual. Enumerating a few here: 1) helps in digesting food that is otherwise not digestible by human gut like digesting xyloglucans by *Bacteroides* [12]. 2) Production of short chain fatty acids by saccharolytic fermentation of non-digestible carbohydrates like formate, lactate, acetate, propionate and butyrate. For instance, Butyrate plays role in maintaining integrity of the layers of gut epithelium mainly intestinal mucosa it accelerates cell division in healthy colorectal cells while maintains control over transformed cells in order to avoid cancer. SCFA also plays role in other factors like immunity, appetite regulation, lipid metabolism, glucose homeostasis [13]. 3) Homeostasis: provide immunity, regulate inflammation, degrade contaminants like heavy metals, pesticides, etc, deactivation of toxins after renal filtration. 4) Immunity: microbiome of gut coevolves with the baby thus our body can differentiate between self and non self microbiota thus helps us evolve adaptive immune system, activates Th cells and t regs in intestine, secrete antimicrobial compound stimulate neutrophil cycling, promote vit d production, over grows pathogenic strains, etc [14].

III. EVIDENCE OF GUT MICROBIOME INTERACTION

More than 20 years ago, the observation of the frequently significant improvement in hepatic encephalopathy patients following the use of oral antibiotics provided the strongest human evidence of a gut microbe-brain interaction [15]. Leaky gut is a feature of hepatic encephalopathy where microbes can pass through the gut barrier and enter the blood stream. As the microbial load rises, ammonia produced by these microbes builds up in the blood, impairing the liver's ability to detoxify it. This results in portosystemic shunting, which is the liver's bypass by our circulatory system, reaching the brain and altering cerebral blood flow, which eventually causes neuroinflammation.

IV. HOW DO PSYCHOBIOTICS WORK?

1. **Directly by establishing in gut:** Dysbiosis, also referred as dysbacteriosis, is defined as an imbalance in the microflora, modifications to their functional makeup and metabolic processes, or changes to their local distribution that disturb the microbiota's equilibrium [16]. Gut dysbiosis has alarming impacts on the individual like due to the connection between age-related dysbiosis and neurological decline and the fact that inflammation is a common factor in a range of age-related illnesses, gut dysbiosis can also play a role in neurodegenerative and cerebrovascular diseases [17]. Autism, Parkinson's disease, pain, sadness, anxiety, and stroke are just a few of the neurological diseases that dysbiosis may help induce or worsen [18]. The pathogenesis of both intestinal and extra-intestinal illnesses has been related to gut dysbiosis like IBD, IBS, and celiac disease are examples of intestinal disorders and allergies, asthma, metabolic syndrome, cardiovascular disease, and obesity are examples of extra-intestinal conditions [19]. Thus, Psychobiotics act as a resolver to the problems imposed by dysbiosis. By completely colonising the gut, utilising all nutrients available and secreting substances known as cytokines that kill or suppress undesirable organisms that would compete with it for nutrients, the gut flora population plays a direct role in protecting against diseases [20]. The cell-density dependent gene

regulator quorum sensing (QS) plays a protective role against intestinal infections. Bacterial regulatory mechanism QS controls both intra- and inter-species communication through the action of chemical substances known as autoinducers (AI).

2. **Indirectly by microbiome-gut brain axis:** Through a bidirectional "microbiome-gut-brain axis," the microbiome and gut interact with the brain, and the brain alternatively interacts with the gut and the microbiome [21].

Microbiome-gut-brain axis involves the following systems:

- CNS - Central Nervous System
- ANS - Autonomic Nervous System
- HPA AXIS - Hypothalamus Pituitary Adrenal Axis
- ENS - Enteric Nervous System
- Gut microbiota

The new area focused here are the ENS and Gut-Microbiome. As per the Society for Neuroscience

The enteric nervous system is a second brain that exists in our digestive tract. This is the origin of the phrase "gut feeling." [22]

- **ENS - Enteric Nervous System:** The third component of the autonomic nervous system is the enteric nervous system. The enteric neural system (ENS) is a sizable portion of the peripheral nervous system (PNS) that has the ability to regulate gastrointestinal function without input from the central nervous system (CNS). Most enteric neurons do not get direct CNS innervation, in contrary to the neurons in sympathetic or parasympathetic ganglia. To integrate information and coordinate motor output, enteric neurons are arranged in microcircuits with intrinsic primary afferent neurons. These neurons can respond intrinsically to regional stimuli. Because it possesses both sensory and motor qualities, the ENS is special and can mediate corrective actions of the CNS; yet, the gut and the CNS typically communicate in a two-way fashion and have an impact on one another. Through the layers of the small and large intestine, the ENS's neurons and glia form a vast network. The inner core or the lumen of the enteric nervous system mucosa, circular muscles, submucosal plexus, and Myenteric plexus and longitudinal muscles in this particular order [23].

- **Vagus nerve:** The vagus nerve controls the gut-brain axis. The 10th cranial nerve is the vagus nerve. It gets its name from the Latin word vagary, which means "wandering," and it's also sometimes called "wandering nerve." It travels from the medulla oblongata in the brain stem down the neck, thorax, and belly. The vagus nerve leaves the skull through the middle compartment of the jugular foramen after leaving the medulla oblongata in the cleft between the inferior cerebellar peduncle. Vagal afferents and vagal efferents are present for the same purposes since it has both sensory and motor functions. In contrast to vagal afferents, which are postganglia, vagal efferents are preganglia. A group of nerve cells outside the central nervous

system, ganglia are ovoid formations. Preganglia are a group of CNS-derived neurons, whereas postganglia develop from ganglia. The ganglia come together to form the plexus.

Vagal efferents (motor functions)

- In the neck, the larynx and pharynx muscles, which control swallowing and vocalisation, are innervated.
- Main parasympathetic supply to the heart is provided in the thorax, which also encourages a decrease in heart rate.
- In the intestine, smooth muscles and glandular secretion are controlled. These muscles arise from the dorsal vagus and innervate the gut's mucosal layers.
- The celiac branch connects the distal portion of the descending colon to the gut.

Abdominal vagal afferents (sensory functions)

- Include sensory endings in the liver and pancreas as well as mucosal mechanreceptors, chemoreceptors, and tension receptors in the oesophagus, stomach, and proximal small intestine.
- Through ganglia, sensory afferents communicate with the NTS-nucleus tractus solitarius, which communicates with the central nervous system. The NTS transmits vagal sensory data to the thalamus, amygdala, locus coeruleus, and rostral ventrolateral medulla, among other areas of the central nervous system (CNS).

The vagus nerve controls vasomotor activity, as well as some reflex motions like coughing, sneezing, swallowing, and vomiting, as well as internal organ processes including digestion, heart rate, and breathing rate. Acetylcholine (ACh) is released at the synaptic junction with secreting cells, intrinsic nerve fibres, and smooth muscles as a result of its activation. ACh induces muscular contractions by binding to nicotinic and muscarinic receptors in the parasympathetic nervous system. The vagus nerve has a remarkable capacity for regeneration, according to animal research [24].

V. PSYCHOBIOTICS FOR PARKINSON'S DISEASE

1. **Targeting dysbiosis and eliminating gut interference:** A connection between PD and gut microbial dysbiosis has been discovered. PD patients were shown to have a significant prevalence of Helicobacter pylori (H. Pylori) infection [25]. Malabsorption syndrome with elevated bacterial density above 105 colony-forming units/mL from small intestine aspirate was also observed along with bloating, flatulence, as well as more intense motor fluctuations [26,27]. A number of bacteria with anti-inflammatory properties, such as those from the genera Blautia, Coprococcus, and Roseburia, significantly decreases in faecal samples from Parkinson's disease (PD) patients. Additionally, the number of bacteria from the genera Faecalibacterium and Ralstonia is decreased and Ralstonia increased in the mucosa of PD subjects, which may cause the colon's microbial balance to shift to a more inflamed state due to the colon's microbial balance [28]. In contrast, Prevotella, Clostridium coccoides, and Bacteroides fragilis are less common in faecal samples from PD patients, according to a different study. Lactobacillus is also

more prevalent. In PD, low Prevotella levels may increase intestinal permeability and reduce mucin production [29]. The prevalence of Prevotellaceae in faeces of PD patients might be reduced by 77.6% when compared to controls, according to a clinical investigation. However, although being highly sensitive, low Prevotellaceae levels alone are not diagnostic of PD [30]. The abundance of Enterobacteriaceae and severity of postural instability & gait problems have also been reported to have a link with gut microbiota, indicating that particular bacteria may be connected to the symptoms or pathophysiology of PD [31]. The genus Bifidobacterium, as well as the bacterial family Enterobacteriaceae, are more abundant in faecal samples from PD patients when compared to match controls. In a similar vein, another study also discovered that the bacterial family Faecalibacterium prausnitzii as well as Lactobacillaceae reduced [32]. Additionally, in faecal samples from PD subjects compared to healthy controls, prospective pathobionts from the subgenus Escherichia-Shigella, Streptococcus, Proteus, and Enterococcus are significantly increased while putative cellulose-degrading bacteria from the genera Blautia, Faecalibacterium, and Ruminococcus are lesser. Streptococcus, in particular, can create neurotoxins such streptomycin and streptokinase, which may cause long-term neurological damage [33]. The study's findings showed that intestinal permeability rose significantly in PD patients and was connected with elevated levels of serum LBP, nitrotyrosine, and Escherichia coli staining in the intestinal mucosa. Additionally, there was a significant association across increased intestinal leakage and tissue oxidative stress, intestinal -synuclein (a PD characteristic), gram-negative bacterial staining, and increased intestinal permeability, indicating a role for gut leakiness in the aetiology of PD. These results seem to confirm Braak's theory that PD may be brought on by an unknown substance that penetrates the intestinal epithelial barrier and causes -synuclein aggregation in the ENS. Furthermore, he proposed that the vagal preganglionic innervation of the gut is a route via which -synuclein pathology appears to spread to the CNS in a way similar to that of prion disease [34]. Increased intestinal barrier permeability may result from changes in intestinal microbial populations. Changes in the composition of the gut microbiota can affect the BBB's permeability. Tight connections keep the BBB's permeability at normal levels [35]. The SN and striatum of PD patients exhibit increased release of inflammatory markers along with microglial activation, astrocyte multiplication, and lymphocyte influx [36]. There is marked decrease in production of short chain fatty acids Since SCFA levels in the intestinal cavity are low and anti-inflammatory activities are suppressed, topical and systemic inflammation is supported. SCFAs also support the development and activation of microglia. Cumulatively these results suggest that changes in microbial metabolites and gut microbial dysbiosis may play a role in the aetiology of Parkinson's disease.

2. **Eliminate interference with drug treatment:** Treatment for PD seeks to reduce the symptoms because there is no known cure.

Because dopamine cannot pass through the blood-brain barrier, medicine is instead administered as a prodrug in the form of the dopamine precursor levodopa, which is converted to dopamine by the tyrosine decarboxylase enzyme inside the brain cells. Levodopa (L-DOPA) is the main medication used in this treatment plan; but, as the condition worsens, its effectiveness decreases. Additionally, it has adverse effects such dyskinesia, which are uncontrollable muscular movements as it converts to dopamine

within gut itself by tyrosine decarboxylase enzyme produced by bacteria of gut and once converted to dopamine it stays as peripheral dopamine as dopamine cannot cross blood brain barrier [37]. Levodopa is also given in combination with carbidopa. To avoid Levodopa being converted to dopamine in the stomach because carbidopa inhibits the tyrosine decarboxylase enzyme generated by the human gut; however, carbidopa itself cannot cross the blood-brain barrier, therefore it cannot impede dopamine conversion in the brain [38]. Tyrosine decarboxylase produced by gut bacteria cannot be inhibited by carbidopa when it is used as a tyrosine decarboxylase inhibitor; it can only inhibit human tyrosine decarboxylase in the gut [39]. Many gut bacterial species, including *Lactobacillus brevis*, *Enterococcus faecalis*, and *Enterococcus faecium*, produce tyrosine decarboxylase enzyme that interferes with medication treatment. As a result, only the brain receives between 5 and 10 percent of the dopamine produced [40,41,42,43]. In order to prevent conversion of levodopa in gut, by gut microflora, such bacteria can be identified within the gut itself which do not produce tyrosine decarboxylase enzyme and will be used to formulate a probiotic that will establish itself within the gut eliminating the interfering strains; thus will not interfere with drug treatment and bioavailability of dopamine to brain will drastically increase thus avoiding frequent increase in drug dosage to pd patients and lengthen the time period.

3. **GABA production:** GABA and Dopamine have opposite effects to each other in a normal functioning brain where dopamine helps in providing movement while GABA keeps it under check in order to control unwanted movement. In PD we externally provide dopamine that does not become available to patient only when required but levodopa converts to dopamine all at once which leads to an overflow of the hormone and gives the side effects in PD that is uncontrolled movement now here GABA inhibiters try to keep movements under control which is successfully done during initial years as usual but as disease progress more dopaminergic cells are lost and so doses increase, so levodopa influx rapidly increases and GABA inhibitors keep on compensating for it and in this process they lose their ability to control unwanted movements or to switch it off. This role explains why these neurotransmitters act as neuromodulators and why do the dyskinesia appear as a major side effect in pd so GABA producing bacteria may help keep in control the unwanted muscle movements [44]. The GABAergic system is disrupted in PD and may be a factor in the early onset of non-motor symptoms [45]. The breakdown of GABA inhibition causes the smooth muscle in the brain arteries to relax. Long-term, this could worsen neurodegenerative processes by altering the blood brain barrier's (BBB) permeability, which could lead to brain tissue and blood vessel inflammation. A compromised or damaged BBB is more vulnerable to inflammatory reactions involving microglia and astrocytes, which may hasten the course of PD [46]. Gamma-aminobutyric acid (GABA) is secreted by Certain strains of Lactobacillus and Bifidobacterium from monosodium glutamate and may show its effect by the gut-brain-axis and so can be used as psychobiotic also GABA can partially cross the gut brain axis therefore apart from transport via the vagus nerve it can also be supplied directly from the gut to brain by blood. Thus, it will help alleviate the major non motor symptoms appearing in pd patients [47,48].

4. **Serotonin*:*** Strong support for the role of the serotonergic system in the pathogenesis underpinning the emergence of motor and non-motor symptoms and consequences in PD

has been revealed by PET molecular imaging. The development of symptoms ranging from tremor and LIDs to depression, weariness, weight loss, and visual hallucinations may be influenced by the non-linear progressive destruction of 5-HT terminals, according to a number of studies. It is hoped that the recent growth in this field of study will transfer into commercial initiatives to create breakthrough therapy approaches for PD.As a solution to it bacteria can be explored for production of serotonin precursor 5HT as serotonin cannot cross BBB its precursor will be directly supplied by gut bacteria via blood also the produced serotonin by gut bacteria stands a chance to be transported to the brain via the microbiome gut brain axis. For instance, *Bifidobacterium infantis (B. infantis)* shows increased levels of the serotonin precursor, tryptophan, in the plasma of rats and can be used as Psychobiotics [49].

5. **Reversal of synucleinopathy:** Study reports that in a validated Caenorhabditis elegans model of synucleinopathy, the *Bacillus subtilis* probiotic strain PXN21 suppresses -synuclein aggregation and clears pre-existing aggregates. Animals of all ages exhibit this protection, which is partially mediated by DAF-16. Numerous B. subtilis strains cause the protective effect via spores and vegetative cells, in part because of the development of a bacterial biofilm in the worms' guts and the production of metabolites. multiple host metabolic pathways, including sphingolipid metabolism, are differentially controlled in response to probiotic administration. the sphingolipid metabolism genes lagr-1, asm-3, and sptl-3 play functional roles in the anti-aggregation effect. these findings lay a foundation for investigating B. subtilis' potential as a dietary supplement for treating diseases [50].

VI. CLINICAL STUDIES

- PD patients were given a probiotic supplement containing *L. acidophilus, B. bifidum, Lactobacillus reuteri*, and *L. fermentum* for 12 weeks in a randomised, double-blind, placebo-controlled clinical trial. The Unified Parkinson's Disease Rating Scale (UPDRS) score of the probiotic eating group was lower than that of the placebo group. Additionally, probiotic use boosted glutathione (GSH) levels while also dramatically lowering hs-CRP and MDA levels. Notably, consuming probiotics dramatically enhanced insulin activity in comparison to a placebo[51].

- One randomised controlled trial examined the genes associated with lipids, insulin, and inflammation in peripheral blood mononuclear cells (PBMCs) from people with Parkinson's disease (PD). After a 12-week intervention, probiotic supplement recipients with Parkinson's disease showed significantly reduced levels of the inflammatory cytokines interleukin-1 (IL-1), interleukin-8 (IL-8), and tumour necrosis factor alpha (TNF-alpha), as well as increased levels of the cytokines transforming growth factor beta (TGF-beta) and peroxisome proliferator-activated receptor gamma (PPAR-gamma) compared to placebo The activation of vascular endothelial growth factor (VEGF), low-density lipoprotein receptor (LDLR), or the markers of inflammation and oxidative stress, however, were not shown to be affected by probiotic consumption[52].

- According to three studies, people with Parkinson's disease who took probiotics had better gastrointestinal health. Constipation was improved in PD patients who had fermented milk containing many different probiotic strains [53].

- Abdominal pain and bloating were greatly reduced when *L. acidophilus* and *B. infantis* were used as probiotics [54].

- Furthermore, following 5 weeks of therapy with fermented milk harbouring *L. casei Shirota,* individuals with PD showed improved bowel habits and stool consistency [55].

- PS128 improved mouse motor impairments brought on by MPTP, increased cortisol, dopaminergic neuronal death, and decreased neurotransmitter levels. Additionally, PS128 reduced oxidative stress, glial hyperactivation, and neuroinflammation in the nigrostriatal pathway and increased levels of NE, neurotrophic factors, and antioxidants. Faecal sample analysis revealed that MPTP-induced Enterobacteriaceae rise and microbial modules associated to LPS and peptidoglycan manufacturing, which had been extensively described in clinical investigations of neurodegenerative disorders, were eased in PS128-fed animals. PS128-fed mice still showed improvements in MPTP neurotoxicity despite PS128 therapy having no effect on the SCFA drop and microbial changes caused by MPTP, indicating a direct protective effect of PS128 on the CNS. This suggests that PS128 may be used as an alternate or additional treatment [56].

- According to studies, employing probiotic bacteria improved the gut's dysbiosis in Parkinson's disease patients [57].

- The UPDRS motor score and quality of life of PD patients were both improved by using PS128 supplements for 12 weeks along with consistent anti-parkinsonian therapy. PS128 might act as a therapeutic adjuvant in the treatment of Parkinson's disease. The effectiveness of PS128 supplementation will eventually need to be further supported by placebo-controlled research [58].

- According to a study, gut dysbiosis affects the aetiology of diseases and predicts their emergence. Furthermore, it was discovered that several Psychobiotics, namely dietary fibres and probiotics from the Lactobacillus family, enhanced various cognitive processes, including cognitive performance and caused a decrease in cortisol response [59].

- *Lactobacillus rhamnosus* treatment in mice boosted GABA brain expression and decreased anxiety and depressive-related behaviour. In in vitro tests on the human colon, a mixed probiotic preparation (*Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus paracasei, and Lactobacillus plantarum*) increased the level of SCFAs Some psychobiotics, which are living bacteria, are thought to help patients with mental illness by encouraging the production of endogenous neurotransmitters like GABA, catecholamines, and 5-HT. Probiotics have been shown to provide advantages for people with Parkinson's disease (PD), including the reduction of constipation and motor symptoms. When taken as a whole, regulating gut

microbiota with probiotics may give the host SCFAs to act as a protective mechanism in PD [60].

- Some SGBs in *Firmicutes*, including *Butyricimonas sp*. CAG:1, *Lachnospira eligens, Clostridiales sp.* CAG:26, etc., increased following probiotic use, according to a study. Additionally, after intervention, the Probio-M8 group's SGBs implicated in SCFA (butyrate, isovaleric acid, and propionate) production increased. According to a paper, Bacteroides produce GABA, and their relative abundance has a bad correlation with the brain patterns linked to depression15. It's interesting to note that more SGBs that encode GABA synthesis modules were detected in the probiotic group, and more Bacteroides intestinalis was discovered in the Probio-M8 group, which was also associated with higher MMSE scores. After the intervention, there were higher SGBs for *Prevotella* and *Lactobacillus* in the placebo group. Prevotella were reported to be more prevalent in PD patients, and they were revealed to be crucial for the metabolism of mucus layer glycoprotein, intestinal barrier permeability, and inflammation50,51. Certain *Lactobacilli* may produce certain enzymes that transform levodopa to dopamine even before reaches the brain, lowering medication efficacy and raising the dosage necessary for therapeutic success. 13,52. In the placebo group, there was a significant correlation between the presence of *L. fermentum* and more severe sickness and a less healthy mental state (measured by higher HAMA and HAMD scores and lower MMSE scores) (showing higher scores of UPDRS). Additionally, after Probio-M8 intervention, some neuroinflammation-related pathogens, including *P. distasonis, Evtepia gabavorous*, and *K. oxytoca*, decreased. *K. oxytoca* was discovered to be significantly and negatively associated with faeces hardness in patients with Parkinson's disease (PD). *K. oxytoca* could induce anxiety and colitis, as well as the demography of apoptotic neuron nerve cells of mice via production of lipopolysaccharide and enterotoxins. Therefore, it seemed likely that Probio-clinical M8's remissive impact was connected to the control of a particular gut flora in PD patients [61].

VII. BENEFITS OF PSYCHOBIOTIC TREATMENT FOR PARKINSON'S DISEASE

- Increases serotonin and GABA.
- Slows or stops development of disease.
- Decreases drug dosage and adaptivity to it.
- Improves quality of life.
- Inhibits pathogenic/harmful/spoilage strains.
- Lengthens course of period.
- Help reduce the symptoms.
- Help overcome the day-to-day struggles faced by PD patients.
- Helps gain control over the disease condition.
- No two Parkinson's are same but Psychobiotics will target the prime affected domains and will be fruitful to treat each different individual.
- Positively influences mood.
- Increases bioavailability of drugs and maximum drug reaches the brain.
- Helps control dysbiosis.
- Reduces the level of dyskinesia.

- Exerts anxiolytic and antidepressant effects slowing changes in emotional and cognitive behavior.
- Indirectly increases immunity and digestion.
- May decrease pro-inflammatory cytokines and oxidative stress.
- Avoids necessity for surgery.

VIII. GAP IN EXISTING RESEARCH [62, 63]

- Individual researches have been carried out on bacterial inhibition and reversal of alpha synuclein formation, dopamine production by bacteria, interference of bacteria in drug treatment, dysbiosis in PD patients and effects of probiotics on Parkinson disease; and on limited scales but till date no probiotic has been formulated by cumulating all the aspects.
- Not much work has been registered on Psychobiotic treatment particularly for Parkinson's disease.
- Evidences of gut-brain-axis and microbial interaction with mental health were only revealed lately near 2015 and the idea of Psychobiotics emerged DE novo near 2018. Most of the articles and research papers date between 2015-2020 so it is still an ongoing research and new domain that is still only partially discovered and requires more work.
- Contrast between young and old individuals in response to similar psychobiotic administrations.
- Administering Psychobiotics at varying concentrations, and comparison of the outcomes.
- Long-term administration of Psychobiotics, followed by analysis of faecal samples for estimation of gut bacteria.
- Effects of different prebiotic on the formulation.
- Tracking psychological and neural during psychobiotic treatment and after cessation of the routine.
- Clinical trials of the adjuvant therapeutic properties of Psychobiotics along with primary drug treatment.
- When do the psychobiotic effect starts to appear and how long does it last?
- How do factors such as diet, genotype, sex, and age moderate the effects of Psychobiotics?
- In-depth study of microbiome-gut-brain axis and effect of microbial influence on mood and cognitive behaviour.
- To understand why do dysbiosis occur?
- Formulation of effective synbiotics.
- monitoring real time gut microbiota
- going beyond bacteria and exploring benefits of archaea, virus of gut.
- Bioprospecting gut bacteria for newer drugs
- Assessing gut microbiota for newer diagnostic techniques to access disease condition
- Designing diet to manage disease
- Personalised nutritional recommendations for individual gut adaptability to attain health

IX. CONCLUSION

Thus, it can be concluded that Parkinson's being incurable and having only one medication therapy needs alternative treatments to fray the state and improve the current situation and no better resort than Psychobiotics as an add on treatment for Parkinson's disease as it acts by manifesting multiple benefits and will be a respite for the PD patients. Also, multiple approaches are made available to target different aspects using specified probiotic species.

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