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PSYCHOBIOTICS; A NEW FRONTIER IN TREATMENT OF DEPRESSION

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Abstract

The gut microbiota is a diverse multitude of bacteria, fungi, protozoa and viruses. The gut- brain axis forms a bilateral pathway between the intestinal microbiome and CNS, its collaborative action having both direct and indirect effect in the body. Intestinal dysbiosis is linked to elevated stress, anxiety and depression which alter the normal functioning. The current paradigm focuses on the effect of probiotics on the neurological disorder and how commensal bacteria can reverse action and alleviate depressive symptoms.Various preclinical and clinical studies have shown evidences suggesting the administration of certain probiotic strains have therapeutic effect in cognitive and behavioural disorders. This article reviews on themutualistic association between the gut- brain axis,impact ofgut microbiota in neurologic disorders and the psychotropic effect of probiotics in depressive patients.

Keywords: Gut microbiome, Psychobiotics, Depression, Gut Brain axis.

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Introduction

Psychobiotics are the live bacteria which release neuroactive substances and thereby confer a mental health benefit, when ingested in appropriate amounts, by influencing the microbial community of the host organism. Although the enteric microbiota is distinct in each individual, the distribution within the intestinal tract and the relative abundance of the bacterial phenotypes is found to be alike. Firmicutes and Bacteroidetes are the major anaerobic microbial communities within the commensal gut bacteria while the lesser abundant groups include Actinobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia [1, 2]. Since it is quite common to observe the emergence of intestinal and neurological disorders coexisting within the same individual, the bidirectional communication of the brain and the gut microbiota is a main area of research interest. Animal studies indicate the interaction of gut microbiota with the central nervous system via the neural, neuroendocrine, neuroimmune and humoral link [1].

An alteration in the gastrointestinal bacterial composition is referred as dysbiosis. It can be causedby various dietary (antibiotics in food and as medicine), lifestyle (stress, physical activity), environmental (contaminants in food) and health factorsand ultimately leads to health problems and disorders affecting the physical, mental and emotional well-being [1]. Supplementation of live bacteria instigate a positive therapeutic and prophylactic outcome on various diseases.

Thevarious effects of psychobioticscan are explained under three categories. Firstly, the psychological impact on the emotional and cognitive processes. Secondly, the aberrant cytokine concentrations, due to the systemic action on the HPA axis, stress hormone response and inflammation, are found to be beneficial in cases such as depression. Thirdly, the neural affects on the crucial

neurotransmitters such as GABA & glutamateand the proteins. GABA, the main inhibitory neurotransmitter in the brain, is involved in the regulation of varying physiological and neurological processes. Since it is secreted by the microorganisms Lactobacillus and Bifidobacterium, a dysbiosis can result in anxiety and depression [1, 3]. Proteins such as the brain-derived neurotrophic factor (BDNF) plays a crucial role in thecognitive processes, spatial learning, elimination of conditioned fear, and object recognition. It is found to be in low levels in anxiety and depression and is reversible through the administration of the antidepressants [3].

Materials and Methods

The literature review for the following article was performed by searching the databases of Science Direct, PubMed, Research Gate, Google Scholar and research paper-based journals using the keywords: probiotics, psychobiotics, gut-brain axis, depression, stress, Suitable information was gathered from these sources and was collated for the devising of this article.

Discussion

Psychobiotics

Psychobiotics is a novel class ofprobiotics used specifically for the neurologicdisorders. They are living organisms which upon sufficient ingestion instil a health benefit to patients suffering from psychiatric illnesses [1]. They are involved in the synthesis and regulation of neurotransmitters and proteins such as GABA, glutamate, serotonin & BDNF, short chain fatty acid (SCFA), establishment of normal microflora, maintenance of beneficialnervus vagus activity, prevention of leaky gut and reduction of potentiating signals from myenteric neurons. Overall they play a key role in controlling the neural excitatory-inhibitory balance, mood and cognitive processes [2].

Characteristics of psychobiotics

The characteristics of psychobiotics include (i). Direct neuro chemical production (GABA, glutamate etc.) by microbe, (ii) Direct activation of gut-brain neural pathways, (iii). Indirect impact on the production of neurotransmitter& proteins, (iv) modulation of neurotrophic chemicals (like BDNF),(v) improvement of nutritional and antioxidant status, (vi)reduction in lipid peroxidation as well as amine or uremic toxin burden, (vii) inhibition of both small intestinal bacterial overgrowth as well as gastric or intestinal pathogens, (viii). Prevention of dysbiosis due to stress, (ix) A decrease in the production of inflammatory cytokine,(x) protection of the intestinal barrier and (x). Limitation of carbohydrate malabsorption [1].

The potential microbial strains used as psychobiotic agents include Bifidobacterium longum and Bifidobacterium infantis. Being present in the intestinal tract, they produce GABA, serotonin precursors and tryptophan. Human clinical studies conducted using probiotic preparation containing Bifidobacterium strains either alone or in combination with other bacteriahave been proven efficacious in the prevention, alleviation or treatment of different pathologies by normalizing the HPA-axis functions and neural functions [3]. The lactic acid producing bacteria (LAPB)-Lactobacillus species and Bifido bacterium are known for their immunomodulatory action. Clostridium butyricum modulates the gut microbiota and produces metabolic SCFA such as acetate, propionate and butyrate and therefore, is capable of exerting beneficial effect in gastrointestinal conditions [4]. Othermicrobes such as Escherichia, Bacillus, Saccharomyces and enterococcus are involved in the production of neurotransmitters especially, noradrenaline.

Gut Brain Axis

The gut microbiota and human host have a symbiotic relationship which is exhibited through a bidirectional communication pathway between the brain and the gut called the gut-brain axis (GBA) [1]. The gut microbes, both directly and indirectly, influence the nervous system. Direct action involves the infiltration of blood vessels by the secreted substances in the gut which leads to stimulation of the vagus nerve by the neuropod cells present in the gut lining. Indirect route involves hormone regulation by the enteroendocrine cells activation, present in the gut lining. Microbes also affect the brain by influencing the immune cells and inflammation [5].

GBA communication network includes the central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axismediated with the help of neuro-immuno-endocrine mediators. The ANS, consisting of sympathetic and parasympathetic pathways, is responsible for the both the transmission of the afferent signals, arising from the lumen, to the CNS via the enteric, spinal & vagal pathways as well as the transmission of the efferent signals from CNS to the intestinal wall [6].

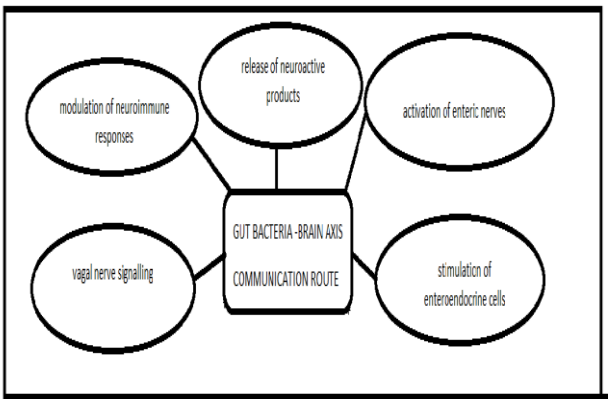

Fig 1.1: Route of Gut Brain axis [1, 7]

Myenteric neurons are located below the enterocytes enabling a direct contact between the microbe and enteric nervous system. Microbiota–ENS interactions play a crucial role as they regulate electrophysiological thresholds and thereby, influence the GBA function. Understanding of this link has been obtained from a recent study in which a subtype of the intrinsic primary afferent neurons of the ENS in adult mice (myenteric after hyperpolarization (AH) neurons),were shown to have reduced cell excitability and reduced duration of the inhibitory slow AH neurons following a single action potential produced by a short current pulse. Additionally, the resting membrane potential and input resistance were found to be altered in GF as compared to SPF mice. GF mice have no commensal intestinal microbiota and as such exhibit an undeveloped immune system however colonization of GF mice with SPF microbiota normalized excitability and reversed the changes on passive membrane [8]. Another study conducted indicated that when Lactobacillus rhamnosus was administered the neurons of the dorsal root ganglion in the colon did not display hyperexcitability in response to noxious [2,6]. Both of these studies pointout that the ENS functioning is regulated by the gut microbe.ENS also confers activation of vagal nerve thereby acting on the CNS.

Main functions of the bidirectional GBA includes–From gut microbiota to brain: Production, expression and turnover of neurotransmitters (i.e.serotonin, GABA) and BDNF, protection of intestinal barrier and tight junction integrity, modulation of enteric sensory afferents, bacterial metabolites, mucosal immune regulation.From brain to gut microbiota: alteration in mucus and biofilm production, in motility, intestinal permeability and in immune function.

Action of Psychobiotics

Immune System

Neuropsychiatric disorders and depression may be caused due to a long-term subjection to raised levels of inflammatory cytokines and persistent changes in neurotransmitter systems. Reports have hypothesized that psychobiotics act on the brain and produce anti-inflammatory actionsby reducing the production of cytokines and stimulate the release of an anti-inflammatory cytokine Interleukin 10[1].The microbiota, through its various elements, interacts with the immune system throughtoll-like receptors (TLRs) which are pattern recognition receptors (PRRs). For instance, the bacterial strains Bifidobacterium infantis and Lactobacillus GG activate the TLR-2 & TLR-4 which leads to the production and increased levels of IL-10, decreased levels of pro-inflammatory cytokines and repair of the impaired BBB permeability due to inflammation & pathogenic pro-inflammatory processes. The pathogen scan also changes the level of neurotransmitters in the brain and also provokes proinflammatory process by inducing prostaglandin synthesis any other way [6]. Thus, we can say that the gut microbiota are key players to a proper immune system development, maintenance, functioning and studies indicatethat dysbiosiscan derail that process and promote inflammation [5].

Short Chain Fatty Acids and Gut Hormones

SCFAs such as acetate, propionate, butyrate & lactate, produced by the gut microbe as a result of the digestion of plant-derived polysaccharide fibres, are absorbed from the colon after which they enter into the systemic circulation and mediate the metabolic functions [7]. Microglia, the primary innate immune effect or cells of CNS, have their morphology, maturation and immunological function regulated by the intestinal microbes by producing SCFAs which interact and ensure the correct functioning and development of microglia [3]. The mechanisms through which the SCFAs exert central effects are firstly, through sparsely located G-protein–coupled receptors in the brain, secondly, by acting as epigenetic modulators through histone deacetylases [1], and thirdly, by crossing the BBB small amounts reach the CNS.

Satiety peptides such as cholecystokinin (CCK), peptidetyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) are released from the gut mucosal enteroendocrine cells and act through FFARs under the influence of the SCFAs. Propionic acid, through activation of FFAR2, mediates the release of GLP-1 and

PYY. Various studies indicate that prebiotic supplementation increases the production of intestinal SCFAs, which in turn modulate enteroendocrine cells and their secretion of PYY and GLP-1. Thus, satiety hormones may play a significant role in the central effects of prebiotics compared to probiotics [3].

Vagus Nerve

The vagus nerve, consisting of sensory (afferent) and motor (efferent) neurons, is responsible for the transmission of information to the brain from various organs present in the abdominal cavity and thereby, helps in the coordination of the parasympathetic activity [3,9]. Nutrition, exercise, and stress have been found to influence the vagal activity. Various evidences suggest that vagal modulation appears to be a common pathway for exerting the vagal effects of antidepressants, anxiolytics, and psychobiotics. Animal studies involving severing of vagus nerve found that the responses to psychobiotic administration were inhibited which concluded that vagus nerve was responsible for mediating the interaction of psychobiotics and their psychophysiological [7].

Neuroactive Agents

Some neurochemicals that have been isolated from gut bacteria are gamma-amino butyric acid (GABA), noradrenaline, serotonin, dopamine, and acetylcholine, which may affect the brain activity directly[10].Serotonin is produced in Enterochromaffin cells (ECs) they are contained in two primary reservoirs: in the intestinal epithelium and enteric neurons . Micro biota accentuates 5-HT biosynthesis from ECs thereby inducing 5-HT modulated GI motility and platelet function. Administering beneficial bacteria that are known to increase serotonin levels in the form of a probiotic or by following a diet that supports bacteria critical for serotonin production may effectively influence mood as well as concomitant GI symptoms [9,10].Gut micro biota plays a prominent role in the generation of free CA in the gut lumen. Biologically active DA and NE were identified in the gut lumen of specific-pathogen-free mice (SPF-M); Ach and enzymes involved in the synthesis of ach was primarily isolated from the Lactobacillus. plantarum . Coordination of GABA and glutamate is essential for the normal functioning of complex brain processes such as neuronal excitability, synaptic plasticity, and cognitive functions such as learning and memory. Moreover, it was found that GABA receptors are present in gut microbiome and that glutamic acid decarboxylase genes are distributed among *Lactobacillus plantarum, Lactobacillus , Bifidobacteriu species* and other gut-derived bacterial species, demonstrating its ability to produce GABA mainly lactic acid bacteria (LAB) [9].

HPA Axis

The HPA axis can be considered as the core stress efferent axis which is responsible for the adaptive responses shown by the organism to any kind of stimuli. when HPA axis become dysfunctional it disrupts the production and function of stress related hormones occurs .Stress as an profound influence on structural and useful aspects of microbiome. Glucocorticoids (corticol, corticosterone) dysregulate gut bacterium operate thereby reducing the integrity of epithelial tissue and allowing outward migration of bacterium and inflammatory immune responses.[1]. Parallelly glucocorticoids also cause suppression of immunosuppressant properties .Cortisol in high concentration cannot exert anti-inflammatory effects thus, down regulating cortisol's negative feedback mechanism on HPA axis is obstructed causing hypercortisolaemia. Imbalance of gut microbiota can cause activation of HPA axis, psychobiotics can restore balance of abnormal stress hormone level. For instance, Ait-Belgnaoui et al. (2014) carried out an experiment in order to identify the response to chronic stress when a probiotic formulation consisting of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 had on the HPA axis was determined.[9] They found that this probiotic supplementation significantly managed to attenuate the HPA axis response to stress.

Depression , Stress ,Anxiety

Since the past two decades, "cytokine theory of depression", has been widely studied. This theory suggests that, an increase in the production of proinflammatory cytokines is associated with the pathophysiology of depression. Indeed, several studies show a significant increase in the production of proinflammatory cytokines (namely, IL-6, IL-1β, IFN-γ, and TNF) among depressed patients [12]. Increase in glucocorticoid level can cause enhanced IL-10 production which in normal situation downregulate HPA axis activity. A phenomenon called "resistance to glucocorticoid action "occurs when glucocorticoid levels raises abnormally, this can cause decrease production of IL-10 which can have serious impact on negative regulation of corticosterone production by adrenal glands and also decrease in IL-10 can instigate imbalance in the cytokine environment which will further activate HPA axis. The composition of the

microbiome can influence the balance of pro- and anti-inflammatory cytokines. It is generally noted that depressed patients often possess an abnormal gut microbiota. Psychosocial stress plays a dominant role within the aetiology of major depression. Activation of the hypothalamic-pituitary adrenal axis by conveyance regarding thebringing about the release of corticotrophin releasing hormone (CRH) and vasopressin (AVP) in conjunction with altered gut barrier perform causes stress. The latter could lead to the passage of lipopolysaccharide and different molecules into the blood with development of a pro-inflammatory makeup, characterised by high interleukin-1 (IL-1) and interleukin-6 (IL-6) levels an autacoid E2 (PGE2) created as a results of immune activation will directly stimulate the ductless gland. Standard antidepressants act directly on m onoamines and additionally suppress inflammatory cytokines. Psychobiotics elevate the anti inflammatory cytokine interleukin 10 (IL-10), decrease pro-inflammatory cytokines, and suppress hypothalamic-pituitary-adrenal axis activity. They additionally act as a delivery vehicle for neuroactive molecules like gamma-amino saturated fatty acid and improve gut barrier perform[2].The over activity of glutamatergic system it can cause degeneration of nerve cells and also GABAergic deficits may contribute to depression .Most connected with depression and anxiety, the tryptophan-kynurenine pathway is considerably influenced by gut microbiota. This can be the opposing pathway for the conversion of tryptophane to 5-hydroxytryptamine, and 5-hydroxytryptamine deficiency was once thought to steer to development of depression and anxiety because of its mood-regulatory operates [13].

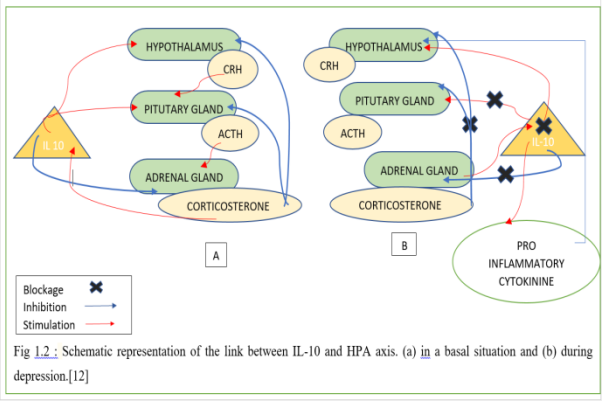

Fig 1.2 : Schematic representation of the link between IL-10 and HPA axis. (a) in a basal situation and (b) during depression.[12]

Probiotics are revolutionizing medicine and are gaining interest as they restore beneficial microbiota and influence behaviour. Psychobiotics may regulate the neurotransmitters and proteins, including gamma-amino butyric acid (GABA), serotonin, glutamate and brain-derived neurotrophic factor (BDNF), which play important roles in controlling the neural excitatory-inhibitory balance, mood, cognitive functions, learning and memory processes [14]. Transplanting abnormal microbiome may even 'transplant' depression.

Human and Animal Studies

Probiotics are revolutionizing medicine and are gaining interest as they restore beneficial microbiota and influence behaviour. Psychobiotics may regulate the neurotransmitters and proteins, including gamma-amino butyric acid (GABA), serotonin, glutamate and brain-derived neurotrophic factor (BDNF), which play important roles in controlling the neural excitatory-inhibitory balance, mood, cognitive functions, learning and memory processes [14]. Transplanting abnormal microbiome may even 'transplant' depression. For instance, researchers transplanted faecal micro biotas from 34 depressed patients and 33 healthy controls into rats who had their gastrointestinal bacteria depleted with a cocktail of antibiotics. Rats that received a transplant from depressed patients showed a dysregulated microbiota and exhibited anhedonic and anxiety-related behaviours compared with those who received a transplant from controls [15]. In the study of Liang et al., the efficacy of *Lactobacillus helveticus* and citalopram (selective serotonin reuptake inhibitor) was compared in various biochemical analyses and anxiety tests (elevated plus maze and open-field test). Psychobiotic-fed rats had lower levels of anxiety and higher memory performance, lower hypothalamo-pituitary activity, and higher anti-inflammatory markers than control group. These findings are similar to citalopram activity [7]. It is noted that intake of Lactobacillus*rhamnosus* (JB-1) is associated with decreased anxiety and depression. Specifically, region-dependent alterations in GABA receptor expression in the brain are seen with consumption of JB-1 as well as reduced plasma corticosterone (CORT) level in BALB/c mice. GABAB1b receptor expression levels decreased in amygdala and hippocampus and increased in cingulate and prelimbic areas in the experiment group. These findings can be interpreted as psychobiotics can exhibit anxiolytic activity by modulating inhibitory neurotransmitter (GABA) functions. Vagotomy was performed on the animals in order to unravel the mechanism of action. This prevented both the emergence of an anxiolytic effect from the probiotic as well as changes in GABA receptor expression. This study provides compelling evidence to indicate that the vagus mediates the behavioural and neurochemical effects of L. rhamnosus. GABA, glutamate, and aspartate levels were found to be high in mice fed with psychobiotics [1, 2, 7, 14]. A Investigation of effect of fermented milk in students with altered cytokine regulation ,immunoglobulin levels ,lymphocyte

function i.e those under academic examination stress. The fermented probiotic milk contained *Lactobacillus delbrueckii bulgaricus*, *Streptococcus salivarius thermophilus*, and *Lactobacillus casei*. The participants were provided with either semi skimmed milk (control) or fermented milk containing yogurt cultures (probiotic) randomly .Speilberger state-trait anxiety inventory (STAI) was used to measure the anxiety.Haematological data of participants were collected , both state-anxiety and trait-anxiety increased from beginning to the end of study. No major differences were observed between probiotic and placebo groups on anxiety measures, but lymphocyte production was increased and maintained the no. of CD-56 cells in the probiotics group, while a decreased production of lymphocytes and natural killer cells were seen in the placebo group. [13, 17].Two of the effective studies conducted performed by Desbonnet et al. In the first study, adult male Sprague-Dawley rats were divided into two groups; 12 for experiment group and 8 for control group and were assessed for the potential benefits of the probiotic B. infantis in the rat maternal separation model of depression used in the study of antidepressant effects. Maternally separated adult rat offspring were put on a long-term treatment with B. infantis and in order to assess motivational state were subjected to the forced swim test.

Table 1.1: Psychobiotics used in neurological disorder [1]

Neurological Condition	Psychobiotic strains
Depression	Lactobacillus spp - L. acidophilus ,L. acidophilus W37, L. brevis W63 , L. casei ,L. casei Shirota , L. casei W56,L. gasseri OLL2809 , L. helveticus NS8 Lactococcusspp - L. lactis W19, L.lactis W58 Bifidobacterium spp - B. infantis, B. bifidum,B. bifidum W23, B. lactis W52, B. longum R0175.

Analysis of the concentrations of cytokine in stimulated whole blood samples, levels of monoamine in the brain, and central & HPA measures, both central and peripheral, were done. Maternal separation reduced swim behaviour and increased immobility in the forced swim test, decreased NE content in the brain, and enhanced proinflammatory peripheral IL-6 release and amygdala corticotrophin-releasing factor mRNA levels. Probiotic treatment resulted in reversal of behavioural deficits, normalization of immune response, and restoration of basal NE concentrations in the brainstem. These results shed light on the role of Bifidobacterium in neural function and suggest that probiotics have influential therapeutic applications. In their second study, the researchers tested the antidepressant activity of this psychobiotic bacterium by comparing it with citalopram (a selective serotonin reuptake inhibitor antidepressant).At the end of the experiment, no difference was found between citalopram and *Bifdobacteriuminfantis* antidepressant activity [2,7]. The administration of a single strain *Bifidobacterium longum* NCC3001 is effective in treating anxiety as well as upregulation in the expression of BDNF in the hippocampus.

Administration of a single strain of *Bacterium infantis* 35624 is effective in treatment of depression-like behaviours, promising animal studies, several have found positive effects of probiotics on mental health in humans. About 22 healthy volunteers administered *Bifidobacterium longum* 1714 and placebo daily four weeks. The volunteers underwent the socially evaluated cold pressor test, which combines psychological and physiological stress, at baseline and after treatment.*B. longum* 1714 appears to reduce the elevated cortisol levels as well as subjective anxiety induced by the cold pressor test compared with placebo. Consuming the psychobiotic also seemed to reduce daily stress reported by the volunteers [4]. Multispecies probiotic supplementation reduced aggressive thoughts, cognitive reactivity to sad mood and depression. Dutch study assessed a [2]. The dutch study enrolled total of 40 individuals among them 20 healthy people without mood disorders who took the probiotic containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24 and *Lactococcus lactis* (W19 and W58) and other 20 took placebo once daily for four weeks. Those who received the probiotic showed reduced overall cognitive reactivity to sad mood on the revised Leiden index of depression sensitivity (LEIDS-r) scale which indicates vulnerability to depression compared to those received placebo [2,15,16,18].

Conclusion

The gut microbiota communicates, through different routes, with the brain via the gut-brain axis and causes both direct and indirect actions. Direct actions involve infiltration of blood vessels and stimulation of vagus nerve whereas indirect action helps in hormone regulation as well as influences immune cells leading to inflammation. Psychobiotics are a novel class in psychopharmacotherapy and is aimed at using probiotics for the treatment of psychiatric disorders. Psychiatric disorder like depression is clinically marked by increased levels of proinflammatory cytokines. Microbiota composition influences the balance of pro- and anti-inflammatory cytokines. Therefore, administration of psychobiotics like Lactobacillus and Bifidobacterium species, known for their immunomodulatory functions, are found to elevate the anti-inflammatory cytokine interleukin 10 (IL-10) due to their interaction with PPRs, decrease proinflammatory

cytokines & thereby reduce neuroinflammation as well as suppress hypothalamic-pituitary-adrenal axis response to stress. Administration of psychobiotics in case of depression and anxiety were found to increase the levels of serotonin which has a profound positive impact on mood. Similarly, administration of Lactobacillus species is associated with increased production of GABA which is essential for the normal functioning of complex brain processes. These probiotics are also found to increase the production of intestinal microbial metabolites such as SCFA which have a significant effect on the neurotransmitters and the behaviour. It is noted that SCFA influences the secretion of PYY and GLP-1 which have brain penetrant properties. Psychobiotics are proven efficacious and are backed by studies conducted on rats which found that psychobiotic-fed rats had lower levels of anxiety and higher memory performance, lower hypothalamo-pituitary activity, and higher anti-inflammatory markers than control group. Modulation of the gut microbiome by consumption of psychobiotics has shown immense potential in the treatment of mental illness so further studies in this area are recommended for providing stronger evidence to understand the power and role of psychobiotics in order the ensure psychobiotics as a more compliant mode of treatment for mental illness .

Glossary

HPA –Hypothalamus –Pituitary –Adrenal Axis, GBA – Gut Brain axis, SCFA – short chain fatty acids, FFAR-Free fatty acid receptor.

Conflict of Interest

Authors are declared No Conflict of Interest

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Author Contribution

All Authors Contributed equally

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Not Applicable

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Not Applicable

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