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REVIEW ARTICLE

The Effect of Probiotic Intervention in Ameliorating the Altered Central Nervous System Functions in Neurological Disorders: A Review

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Abstract: There has been a significant rise in the occurrence of various neurological ailments worldwide. The need to investigate newer and safer intervention therapies with prophylactic and/or therapeutic effects is well understood. Probiotics have recently been shown to hold promise as an intervention option that warrants future work. Probiotic strains have shown beneficial treatment outcomes as evidenced in various animal and human studies. Although numerous articles have highlighted the role of gut microbiota and its cross-talk with human brain in modulating Central Nervous System (CNS) physiology and neurochemistry, the present review solely focuses on the ability of externally administered probiotic strains (that may or may not be part of the already existing gut microflora of an average human) in ameliorating the altered CNS functions in patients. The review aims at giving a comprehensive analysis of the studies performed on animals and humans and discusses the findings in different neurological and psychiatric disorders (Anxiety, Major Depressive disorder, bipolar disorder, schizophrenia, autism spectrum disorder, cognitive impairments *etc*). The article also highlights different mechanisms through which the probiotic bacteria operate in improving neurologic manifestations or decreasing the incidence of neurological disorders. These underlying mechanisms include both direct as well as indirect pathways involving neural, hormonal and immunological pathways. The potential of probiotics as an important dietary modification as well as a useful intervention therapy with preventive and therapeutic value for the target population holds strong. However, future evaluation into formulation designing, selecting the best probiotic strain(s) for each specific disease and safety and tolerability aspects in patients needs to be considered.

Keywords: Gut Microbiota, Probiotics, Gut–brain axis, Neurological disorders, Homeostasis, Depression.

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1. INTRODUCTION

The term gut microbiota, is characterized by the complex population of micro-organisms found within the mammalian gastrointestinal tract. This vast complexity of the gut ecosystem that includes fungi, bacteria, viruses and protozoans, collectively weigh up to 2kg. Presently, the gut has become a subject of broad research as scientists allude and treat the human intestine as an organ. Almost a hundred trillion microbes present in the gut play a crucial role in influencing nutrition [1], physiology [2], metabolism [3] and immunity [4, 5]. Recently, scientists have shown the relationship between diversity and complexity of the gut microbiota and proper functioning of human brains [6, 7]. A study by a group of scientists [8 - 10] indicated that germ free mice are more susceptible to stress-related disorders. Thus, our gut microbiota influences anxiety, depression and other stress related behaviours [9, 11, 12]. These mood altering bacteria have presently been referred as "psychobiotics" due to their ability to produce hundreds of neurochemicals that influence the brain in a positive way [13]. For example, Serotonin which is the "happy" hormone that impacts mood, anxiety and happiness, is primarily (approximately 95%) produced in our gut (*i.e* our second brain) [14] and its production is regulated by these gut bacteria. The quality and number of gut bacteria differ in the composition in individuals suffering from chronic mental ailments, such as depression, mood and anxiety disorders, cognition related disorders *etc*. as compared to the healthy population as evidenced by past studies [15, 16].

However, the great news is that our gut micro-environments are not static but malleable. Therefore, strengthening our gut may be the next clue to a healthy and happy state of mind. One of the healthy ways to change the gut microbiota towards the healthy side is through the continued intake of probiotics. Probiotics defined as "live micro-organisms which confer a health benefit on the host" help in maintaining a healthy gut. Probiotics that change the population of gut bacteria, have also been shown to alleviate the range of neurological conditions and influence brain activity related to emotion regulation and mood up-liftment [17]. Also, probiotics work hand in hand with prebiotics, which

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are non-digestible natural food components, in promoting the growth and activity of gut bacteria [18]. Mind-altering bacteria residing in our gut need to be replenished frequently and therefore, regular consumption of probiotic and pre-biotic rich foods should be an essential part of our daily schedule. This will help in restoring and maintaining the gut microbial population and thus produce benefits for the host in the context of neurologic diseases.

The present review article focus on the ability of probiotics to positively influence our CNS functions in ameliorating the altered brain functionality seen during different neurological and psychiatric ailments. The study highlights both preclinical and clinical findings (animal and human subjects) of past workers and summarizes the possible mechanism(s) through which the probiotic strains have shown to alter brain biochemistry. The potential role of probiotics in acting both as a therapeutic as well as a prophylactic option holds strong and represents an important dietary modification which, when followed in a disciplined manner, helps in maintaining homeostasis towards sound mental health and a calmer state of mind.

2. OVERVIEW OF MENTAL AILMENTS: ALARMING STATISTICS

According to the WHO and Centre for Disease Control and Prevention (CDC), the mental disease may be defined as a condition that impacts an individual's thought process, emotions or behaviour leading to dysregulation of mood [19]. The mental ailments affecting the central and peripheral nervous system can be broadly categorized into two main types: a) neurological disorders and b) neuropsychiatric disorders. Neurological disorders originate both due to damage and degeneration leading to malfunctioning of the brain, spinal cord and nerves. These include structural disorders due to brain or spinal cord injury, functional disorders due to improper functioning of the brain such as epilepsy, neuralgia *etc*., degenerative disorders due to death or damage of nerve cells (Parkinson's, Alzheimer's disease), genetic disorders and CNS infections. Neuropsychiatric disorders involve altered functioning of mood, behavior, memory, body control and may originate from both physical and emotional factors and/or underlying neurological disorders that may later manifest as a psychiatric disorder. Different types of neuropsychiatric disorders include depression, schizophrenia, bipolar affective disorder, anxiety disorders, attention deficit disorders, attention deficit hyperactivity disorder *etc*. Mental diseases are usually common in children, females, elderly, disaster survivors, industrial workers, adolescents and chronic patients. Compared to men, due to various factors such as gender discrimination, early marriage, domestic violence, and rapid social change, women are at high risk to develop mental illness as compared to men. Below are few facts and statistics associated with different mental ailments along with its status especially in India:

- One in the four people in the world will be affected by mental or neurological disorders at some point in their lives. Around 450 million people suffer from such conditions, placing mental disorders among the leading causes of ill-health and disability worldwide [20].
- According to the Centre for Disease Control (CDC), depression is the most common mental disorder affecting more than 26% of the U.S adult population. It has been estimated that by 2020, depression is going to be the second leading disability worldwide [21].
- According to a recent study, done to assess the rate of mental disorders, the prevalence of mental disorders (depression, anxiety, post-traumatic stress disorder, bipolar disorder, and schizophrenia) was 22·1% at any point in time in the conflict-affected populations [22].
- As per a study conducted from 1983-2013 by Steel *et al*. [23], a consistent gender effect in the prevalence of common mental disorder was evident; women having higher rates of mood disorders and men having higher rates of substance use disorders.
- People suffering from depression have a higher risk (40%) of developing cardiovascular and metabolic diseases than the general population. People with serious mental illness are nearly twice as likely to develop these conditions [24].
- A study conducted by the National Commission on Macroeconomics and Health in 2005, reported that nearly 5% of India's population suffers from common mental disorders, like depression and anxiety [25].
- According to the survey of epidemiological studies done in 2000, the predominance of mental illness was 70.5 per 1000 in rural and 73 per 1000 in the urban population in India [25].
- India needs to talk about mental illness as 13.7 percent of India's general population is suffering from mental problem, according to a countrywide National Institute of Mental Health & Neurosciences (Nimhans) study [26].The occurrence of mental disorders has been observed in low-income group particularly 30–49 age groups or over 60. Urban areas are mostly affected with differing kinds of mental disorders predominantly schizophrenia, mood disorders and neurotic- or stress-related disorders [27].
- About 80 per cent of people experiencing severe mental disorders don't reveal their illness because of the stigma attached to mental illness resulting in huge treatment gaps and worsening of the condition [28].

This statistics highlights the need to focus on healthy alternatives and use of preventive and prophylactic measures to be adopted right from the early age so as to strengthen the brain and related system in maintaining homeostasis thereby preventing the onset, decreasing the frequency of relapse and/or relieving the symptoms associated with neurological disorders.

3. ROLE OF GUT FLORA: THE GUT-BRAIN CONNECTION

The gut microbiota inhabits the largest numbers of bacteria and the greatest number of species that have co-evolved with the human body over thousands of years to form a complex symbiotic relationship [29]. The gut microbiota is also important for the development of both the intestinal mucosal barrier and the systemic immune system in humans that

provides a barrier to pathogenic organisms. By fully colonizing the attachment sites, utilization of all available nutrients, and by secreting antimicrobial compounds, the gut flora community plays a direct role in defending against pathogens. Disruption of the gut flora leads to the establishment of other xenobiotics such as like *Clostridium difficle* which otherwise are kept in abeyance [30]. Colonic bacteria apart from expressing carbohydrate fermenting enzymes, which provide them with the ability to ferment complex carbohydrates, can also metabolize phytochemicals and food toxicants. Studies revealed that gut microbiota can metabolize more than 30 drugs [31].There exists a complex communication system between the gut microbiota, and the brain through biochemical signaling called the gut-brain axis. It is the bidirectional communication between CNS and the digestive system. It involves the participation of these components: the central nervous system, the hypothalamic–pituitary–adrenal axis (HPA axis), the autonomic nervous system (sympathetic and parasympathetic), the enteric nervous system and finally the gut microbiota [32]. To date, past workers have focused on studying the role of the gut-brain axis in animals, or on characterizing the various neuroactive compounds that gut flora can produce [33, 34]. Studies with humans – measuring variations in gut flora between people with various psychiatric and neurological conditions or when stressed, or measuring effects of various probiotics (dubbed "psychobiotics" in this context) – gave useful insight into the role of gut microbes in the current interplay. Whether changes to gut flora are a result of disease, a cause of disease, or both in any number of possible feedback loops in the gut-brain axis, warrant more work.

The first interest in the field was sparked by a group of Japanese scientists in their study [35] where they exhibited that germ-free mice (devoid of intestinal flora) showed an exaggerated response to stress. This gave a clear indication that gut flora has properties to alleviate stress and anxiety responses. It was also shown that maternal separation for rats was linked to changes in gut flora and elevated neonatal stress seen with stress and anxiety-like behavior in such rats [12]. People with schizophrenia and Parkinsons disease have altered gut flora and also tend to have more gastrointestinal problems as compared to healthy counterparts [36]. Also, around 70% of people with autism have also gastrointestinal problems indicating that there may be a connection between autism and gut flora [37]. Some studies have found differences in the gut flora of children with autism spectrum disorder as compared with children without autism. There are many pathways and molecules through which our gut flora affects our brain and its functioning. Gut flora produces a range of neuroactive molecules, such as acetylcholine, catecholamines, γ-aminoculesbutyricacid, histamine, melatonin, and serotonin, which are all essential for regulating normal brain homeostasis [38]. Gut flora produces a range of circulating cytokines, some of which affect brain function [36]. The gut flora also release various neuroactive molecules such as serotonin (the master happiness molecule) that can directly activate the vagus nerve, which transmits information to the brain [39, 40]. Many neurologists and psychiatrists now realize that this may be the reason that antidepressants are often less effective in treating depression than proper dietary changes. In addition, GABA which stands for gamma-amino butyric acid is an amino acid produced by gut bacteria that calms nerve activity. It does this by inhibiting transmissions and normalizing brain waves, so that the nervous system returns back to a steadier state after it's been excited by stress [13, 38, 41]. It is calming amino acid essential for deep sleep and gut flora help to maintain its level at an optimal state. Moreover, Glutamate, a neurotransmitter also produced by gut bacteria, is involved in cognition, learning, and memory. It is abundant in a healthy brain. However, in conditions such as depression, anxiety disorders, Alzheimer's – both GABA and glutamate levels are below normal [42]. These mechanisms clearly show the protective and beneficial role of our healthy gut bacteria in maintaining a sound mental state of mind that is the key to happiness and health.

4. STRENGTHEN THE GUT MICROBIOTA: ROLE OF PROBIOTICS

Studies show a clear indication that lack of healthy gut microbes is linked to mental ailments, such as depression and anxiety disorders indicating the importance of good bacteria in maintaining homeostasis at the brain level [43, 44]. The good news is that our gut micro-environments are malleable. Therefore, strengthening our gut may be the next clue to a healthy and happy state of mind.

4.1. Probiotics: An Overview

Probiotics defined as "live micro-organisms which confer a health benefit on the host" help in maintaining healthy gut. Probiotics that change the population of gut bacteria, have also been shown to alleviate depression and influence brain activity related to emotion regulation and mood upliftment, motivation, reward, and happiness. The probiotic bacteria used in commercial products today are mainly members of the genera *Lactobacillus* and *Bifido bacterium*. *Lactobacillus* species from which probiotic strains have been isolated include *L. acidophilus, Lactobacilllus johnsonii, Lactobacilllus casei, Lactobacilllus rhamnosus, Lactobacilllus gasseri,* and *Lactobacilllus reuteri*. *Bifidobacterium* strains include *Bifidobacterium bifidum, Bifidobacterium longum,* and *Bifidobacterium infantis* [45 - 47].

There are various types of probiotic supplements [48, 49] which can help us in maintaining our health like in the form of:

Capsules – these are one of the most common and convenient forms of probiotic supplements found in the health food store.

Chewables – primarily for children, chewable tablets contain a variety of different organisms in a convenient, chewable format for those people who are not so fond of swallowing pills.

Liquids – These probiotics are unstable at higher (warm) temperatures, and are therefore kept at refrigeration. Also, liquid probiotics are the freshest, easiest, and most potent form especially for people who can't swallow pills.

Probiotic Drinks – From kefir water to probiotic juices, there are a number of drinkables that claim to have probiotics

in them. Though, it is important to check labels. Many of the juice drinks only contain a few (as in three or four) strains of probiotics, compared to the dozens of strains many quality capsule probiotic supplements contain.

Powders – Powdered probiotics are another common format for friendly bacteria. The great thing about powders is the ability to incorporate them into all kinds of substances, including juices, yogurt, applesauce, *etc*.

Probiotic foods – It includes different kinds of fermented food products having a live bacterial culture which can be consumed. These include:

Kefir – Similar to yogurt, this fermented dairy product is a unique combination of milk and fermented kefir grains. It has a slightly acidic and tart flavor and contains anywhere from 10 to 34 strains of probiotics.

Cultured Vegetables (Sauerkraut and Kimchi) – Sauerkraut is made from fermented cabbage and is high in organic acids (what gives food its sour taste) which supports the growth of good bacteria. Kimchi is a cousin to sauerkraut and is the Korean take on cultured veggies.

Kombucha – It is produced by an effervescent fermentation of black tea that is started by using a symbiotic colony of bacteria and yeast (SCOBY).

Coconut Kefir – Made by fermenting the juice of young coconuts with kefir grains.

Natto – A popular dish consisting of fermented soybeans. Natto contains the extremely powerful probiotic *Bacillus subtilis*.

Yogurt – The most popular probiotic food is live cultured yogurt or greek yogurt made from the milk of cows, goats, or sheep that has been fermented by *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*.

Miso-Soybeans fermented with brown rice produce miso paste, a popular seasoning used in Asian cuisine. The fermentation process is what makes this condiment a source of *Lactobacillus acidophilus*.

Tempeh-Another food formed from fermented soybeans, tempeh is a firm, white block that's frequently used as a protein-packed meat substitute for vegans and vegetarians. Keeping in mind, it has more calories - but more protein, fiber and probiotic potential - than tofu, which is also soy-based.

4.2. Evidence From Animal Studies

Gut bacteria can communicate with the host through the microbiota-gut-brain axis (which mainly includes the immune, neuroendocrine, and neural pathways) to influence brain and behavior. This has been proved in numerous pre-clinical studies in animal subjects whereby continuous administration of probiotics showed significant improvement in biochemical parameters associated with the disease progression, relieving the symptoms and behavioral defects. Although a large number of animal studies have been cited and reported, the table below has discussed the major studies targeting a different set of mental ailments (Table **1**).

Table 1. Animal studies on evaluating the effects of Probiotics on Central Nervous System functions in various disease conditions

Disease target & Study	Objective	Animal	Treatment /Intervention	Outcome	Conclusion
Depression [50]	To study psychotropic effects of a potential psychobiotic bacterium, *Lactobacillus plantarum* strain PS128 (PS128), on mice subjected to early life stress (ELS) and on naïve adult mice.	ELS mice Naïve mice	*L. plantarum* PS128 10^9 28 days	Behavioral tests revealed that chronic ingestion of PS128 increased the locomotor activities in both ELS and naïve adult mice in the open field test. In the elevated plus maze, PS128 significantly reduced the anxiety-like behaviors in naïve adult mice but not in the ELS mice; whereas the depression-like behaviors were reduced in ELS mice but not in naïve mice in forced swimming test and sucrose preference test.	Chronic ingestion of PS128 could ameliorate anxiety- and depression-like behaviors and modulate neurochemicals and has great potential for improving stress-related symptoms.
Stress related Anxiety Disorder [51]	To study the effect of administration of *Lactobacillus helveticus* NS8 on behavioural, cognitive and biochemical aberrations caused by chronic restraint stress in SPF rats	SPF CRS Rats	*L. helveticus* NS8 (10^9 CFU/ml) for 21 days	*L. helveticus* NS8 improved cognitive dysfunction and behaviour anxiety and depression with decrease in CPRT levels, ACTH levels, increase in IL-10 levels and restored levels of 5-HT and NE.	Probiotic bacteria represents a potential target in relieving stress related behavioural problems.
Alzheimer's [52]	To study the effect of probiotic supplementation for 6 weeks in beta-amyloid induced rat model of Alzheimer's disease (AD)	Rats Beta-amyloid induced rat model	500 mg probiotic given daily by gavage for 4 weeks before and 2 weeks after beta-amyloid(1-42) administration	Probiotic supplementation improved learning but not memory impairment, increase levels of PPF ratios were seen compared to the placebo group.	Positive impact of probiotic administration on learning capacity and LTP in rats with AD like symptoms.

(Table 1) contd.....

Disease target & Study	Objective	Animal	Treatment /Intervention	Outcome	Conclusion
Depression [53]	To study the effect of *Bifidobacterium infantis* in maternal separation model of depression	Rats (Rat maternal separation model)	Adult rat offsprings chronically treated with Citaopram or Bifidobacteria and then subjected to forced Swim test (FST)	Probiotic treatment helped in normalisation of immune response, reversal of behavioural deficits, restored the noradrenaline levels in brains	Potential therapeutic target to treat the symptom of depression
Autism spectrum disorder (ASD) [54]	To study the gut-microbiota connection in a mouse model of ASD	Offspring mice (model of maternal immune activation; MIA)	*Bacteriodes fraglis* NCTC9343;10^{10} 6 days	*Bacteriodes fraglis* oral administration corrected gut permeability, ameliorates defects in anxiety and sensorimotor behavior in offspring mice	Potential probiotic therapy for targeting autism defects and behavioral symptom display at an early age
Chronic fatigue syndrome (CFS) [55]	To study the role of *Lactobacillus acidophilus* loaded floating alginate beads in improving chronic fatigue syndrome (CFS)	Rats	Per-oral administration of free LAB and LAB loaded alginate beads daily for 28 days (10^{7} CFU/ml)	Treatment with Lab and LAB loaded beads significantly decreased TNF-alpha levels, decrease in immobility and decrease in post swim fatigue during the *f*orced swim test assay in animals.	Valuable therapeutic role of LAB loaded alginate beads in the treatment against CFS.
Vascular Dementia (VaD) [56]	To study the effect of administration of *C.butyricum*	VaD mice	*C. butyricum WZMC1016 (CGMCC 9831)*	*C. butyricum* significantly attenuated the cognitive dysfunction and histopathological damage seen in VAD mice while decreasing the neuronal apoptosis and increased BDNF levels.	Probiotic administration is a potential new therapeutic option to treat this disease

CORT, corticosterone; 5-HT, 5-hydroxytryptamine; ACTH, adrenocorticotropic hormone; NE, norepinephrine; BDNF, brain-derived neurotrophic factor; GABA, gamma-Aminobutyric acid; CFS, chronic fatigue syndrome; LAB, *Lactobacillus acidophilus*; VaD, vascular dementia; NF-κB, nuclear factor-kappa B; MIA, maternal immune activation; TNF: tumor necrosis factor; SPF:specific pathogen free

4.3. Evidence From Human Studies

Besides animal data, studies on human subjects have also been reported. In most of the available studies, two major strains *i.e. Bifidobacterium* and *Lactobacillus* preparations have been used and findings point toward a positive effect in improving the CNS related functions both as a preventive therapy as well as a therapeutic option.

Benton *et al*. [57] discussed the findings of a randomized trial in which 132 healthy members of the general population received a probiotic containing milk drink daily for a 3-week period. Mood and cognition were measured at baseline and after 10 and 20 days of consumption. The results indicated that the group that initially reported a poor mood showed improvement in their mood after consuming the probiotic-containing milk drink.

In another pilot study [58], 39 patients suffering from Chronic Ftigue Syndrome (CFS) were randomized and received *Lactobacillus casei* strain Shirota (LcS) or a placebo daily for two months. Results showed a significant rise in both Lactobacillus and Bifidobacteria and a simultaneous significant decrease in anxiety symptoms among those taking the probiotic *vs* controls ($p = 0.01$). These results further support the role of a gut-brain interface, which is capable of significantly interacting with the brain bio-chemicals and thus can modulate the disease outcomes.

Masaoudi *et al*. [59] carried out testing in both rats as well as human volunteers. In the preclinical study, rats were daily administered probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) for 2 weeks and subsequently tested in a screening model. In the clinical trial, volunteers participated in a double-blind, placebo-controlled, randomized group study with Probiotic Formulation (PF) administered for 30 days and later assessed. Daily sub-chronic administration of PF significantly reduced anxiety-like behavior in rats ($P < 0.05$) and alleviated psychological distress in volunteers as well.

In another randomized placebo controlled trial [60], the effect of probiotic supplementation on schizophrenia symptoms was studied. Following a 2-week placebo run-in period, patients were randomly assigned to 14 weeks of double-blind adjunctive probiotic (*Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. lactis strain Bb12) or placebo therapy. However, results depicted no significant change in relieving the typical symptoms but probiotic supplementation proved to reduce the development of severe bowel difficulties associated with schizophrenia.

Steenbergen and co-workers [61] reported in their study carried out as a triple-blind, placebo-controlled, randomized trial where 20 healthy participants with current mood disorder received a 4-week probiotic food-supplement intervention with the multispecies probiotics, while 20 control participants received an inert placebo for the same period. Compared to the participants who received the placebo intervention, participants who received the 4-week multispecies probiotics intervention showed a significantly reduced overall cognitive reactivity to sad mood. These results provided a direct evidence that the intake of probiotics may help reduce negative thoughts associated with a sad mood.

Mohammaddi *et al*. [62] reported in another double-blind placebo controlled study where the effect of intake of probiotic yogurt on the mental health of 70 petrochemical workers was evaluated. Subjects were randomly divided into three groups to

receive 100 g/day probiotic yogurt + one placebo capsule (n = 25) or one probiotic capsule daily + 100 g/day conventional yogurt (n = 25) or 100 g/day conventional yogurt + one placebo capsule (n = 20) for 6 weeks. Mental health parameters, including a general health questionnaire (GHQ) and depression anxiety and stress scale (DASS) scores were measured. After six weeks of intervention, a significant improvement of major parameters was seen in the probiotic yogurt group.

In a yet interesting study, Takada *et al*. [63] studied the role of probiotic *Lactobacillus casei* strain Shirota in relieving stress-associated symptoms before examinations. Three double-blind, placebo-controlled trials were conducted to examine the effects of LcS on psychological and physiological stress responses in healthy medical students under academic examination stress. Subjects received LcS-fermented milk or placebo daily for 8 weeks before taking a national standardized examination. Subjective anxiety scores, salivary cortisol levels, and the presence of physical symptoms during the intervention were pooled and analyzed. Findings suggest that LcS may prevent hyper-secretion of cortisol and physical symptoms under stressful conditions, possibly through vagal afferent signaling to the brain.

4.4. Efect of Probiotocs on CNS: Mechanisms Involved

It is evident from various animal and human studies that our gut microbiota has a strong influence on CNS functions and probiotics can alter the gut microbiota composition in favor of a better mental state. Probiotic bacteria exert a positive effect on the brain biochemistry at various levels *via* both a direct and indirect mechanism that are summarized below:

4.4.1. Restoration of HPA Axis Function (CORT, ACTH Levels)

The Hypothalamic Pituitary Adrenal (**HPA**) Axis is our central stress response system. HPA axis acts as a major endocrine system that consists of three components: the hypothalamus; the pituitary gland and the adrenal gland. It plays a key role indirectly being involved in neurology of an array of mood disorders, such as anxiety disorders, bipolar disorder, insomnia, major depressive disorder, chronic fatigue syndrome, irritable bowel syndrome *etc*. It has been reported that most of the antidepressants help to regulate and restore the HPA function [64, 65].Studies have reported that repeated or chronic stress leads to hyperactivity of the HPA axis with elevated cortisol levels especially are seen with people suffering from psychotic disorders, major depressive disorders, bipolar disorder [66 - 69]. HPA axis activation appears to have a prognostic value and is associated with an increased risk of depression relapse and even suicide [66, 70]. Therefore, one of the targets for intervention, therapy, must be an agent capable of restoring and normalizing the HPA axis which gets altered in different neurological disorders. Studies have indicated that many lactobacillus species (*L. plantarum, L. helveticus,L. rhamnosus, and L. casei)* and Bifidobacterium species *(B. infantis, B. longum*) are capable of significantly reducing the heightened HPA axis by decreasing the cortisol (CORT) and/or adrenocorticotropic hormone (ACTH) levels [56, 71 - 74].

Cortisol, the main glucocorticoid in humans is lipophilic and can easily cross the blood-brain barrier. It has been directly involved in effects on mood, stress, anxiety, sleep as well as cognition [75 - 77]. Ouanes and Popp [78] reported that very high cortisol levels in the elderly are linked to an increased risk of dementia and Alzheimer's disease. Also, high levels of cortisol have been associated with hippocampal atrophy which is further linked with many neurological conditions. Probiotic strains help to restore the heightened activity of cortisol (CORT levels) in many of the mood disorders as evidenced by past studies [41, 63, 78 - 80]. Gareau *et al*. [81] reported the findings that the probiotic strain of Lactobacillus species was able to normalize the elevated HPA axis activation following maternal separation in rats pups with a simultaneous decrease in CORT levels following administration for 20 days. A similar effect was seen in a rat model of irritable bowel syndrome as the two strains (*Bifidobacterium animalis*, *Propionibacterium jensenii*) were able to restore the heightened CORT levels and associated HPA axis function [82].

4.4.2. Brain-derived Neurotrophic Factor (BDNF) Up-regulation and SCFA Production

Neurotrophic factors represent a class of proteins that play an essential role in controlling neuronal function and maintaining cellular integrity, the survival of nerve cells, their differentiation and maintaining synaptic plasticity [83, 84]. BDNF is one of the well-conserved neurotrophic factors studied to date. Dys-regulation of BDNF expression with decreased serum and plasma levels of BDNF protein has been seen in an array of neuro-degenerative disorders as well as psychiatric disorders such as bipolar disorder, major depressive disorder, schizophrenia, epilepsy *etc* [85 - 89]. Ranuh *et al*. [90] recently showed a direct link between the up-regulation of brain BDNF levels by probiotic *Lactobacillus plantarum* IS-10506. Besides this, additional studies also show the evidence of the ability of probiotics in up-regulating the BDNF, stimulating the gut-brain axis while promoting brain development differentiation, memory and brain plasticity [91 - 93].BDNF is capable of exerting a positive effect on the gut-bran axis through butyrate production that can be used as an adjunct therapy in cognitive impairment associated with old age. Butyrate is a Short-Chain Fatty Acid (SCFA) that has another effect on the suppression of the levels of pro-inflammatory cytokines which are heightened in various mood and psychiatric disorders [94 - 96]. Intestinal microbiota produces a substantial amount of this SCFA in the human gut [97 - 99]. Butyrate also increases the expression of a very important antioxidant enzyme (Glutathione, GSH) which helps to decrease the oxidative stress one of the neurodegenerative factors to be considered [100, 101].

4.4.3. C-fos Expression:

Activation of proto oncogene c-fos in the brain has been described by past workers and its expression is up-regulated during psychiatric disorders such as seizure activity, noxious termination of the spinal cord [102 - 104]. c-fos over-expression in the hippocampus in cases of Alzheimer's disease and dementia have also been reported [105, 106]. C-fos is an immediate early gene and it's changed in the expression has

been directly associated with disorders of learning, memory, cognition, psychosis, *etc* [107 - 112]. Smith *et al*. [113] reported that probiotic treatment was able to restore the hippocampal c-fos expression in mice exposed to psychological stress. The combination of *Lactobacillus rhamnosus* and *Lactobacillus helveticus* have been shown to improve the c-fos expression in the hippocampus and associated memory response [81, 114]. C-fos is one of the direct mechanisms involved in the homeostasis of the altered brain biochemistry by the probiotic strains.

4.4.4. Through Vagus Nerve:

The vagus nerve represents the main component of the parasympathetic nervous system, which is an important connection between the brain and the gastrointestinal tract. Evidence indicates that vagus nerve stimulation exhibits a promising add-on option for the treatment of depression, post-traumatic stress disorder, and inflammatory bowel disease [115 - 118]. It has an inhibitory action on the production of pro-inflammatory cytokines and TNF-α, which are increased in clinical depression, and a corresponding stimulatory action on the production of anti-inflammatory compounds. Finally, vagal nerve stimulation decreases corticotropin releasing hormone to modulate the HPA axis [119, 120]. Collectively, these actions positively affect mood and psychological state. One of the direct effects of probiotics is through the interaction with the vagus and enteric nerves that play a crucial role in gut-brain axis activity. It is evident from studies done on vagotomised animals that when *Lactobacillus rhamnosus* administered to such animals, no effect was observed on their CNS functions as the strains were unable to bring any effect on neuro-chemical and behavioral changes in such animals [41]. In line with that, in a model of chronic colitis associated with anxiety-like behavior, the anxiolytic effect obtained with treatment with *Bifidobacterium longum*, was absent in mice that were vagotomized before the induction of colitis [74]. Also, *Lactobacillus casei* showed the effect by increasing the gastric vagal afferent activity [63]. Also, a healthy microbiota produces copious amounts of short-chain fatty acids, such as butyric acid, which directly activate afferent vagal terminals and send messages from the gut to the brain [120]

Besides this, neurotransmitters such as dopamine (DA), serotonin (5-Hydroxy tryptophan;5-HT) that play a key role in most of the mood and behavioral disorders and chronic depression episodes have been altered and restored to their normal state by probiotic strains. Among the indirect pathways, it was found that certain *Lactobacillus* and *Bifidobacteria* strains enhance the precursor of 5-HT that is serum tryptophan [121, 122].Also, most probiotics are capable of altering our immune system limiting the pro-inflammatory cytokines levels (IL-6, IL-1, TNF-α.) and increasing the production of anti-inflammatory cytokines (IL-10) which have a direct effect on the nervous system as these pro-inflammatory cytokines, along with IL-2 and IL-1β, are key participants in depressive states and other affective disorders [51, 54, 123 - 127].These immune-effective probiotics were *L. plantarum, L. helveticus, L. fermentum, L. acidophilus, B. longum, and L. rhamnosus*. Other indirect pathway includes the ability of probiotics to restore the intestinal permeability. Intestinal barrier permeability gets disrupted in many disease states (by toxins produced by pathogenic bacteria). This leads to increased gut permeability, thus causing increased translocation of gut bacteria and their bacterial products (LPS, neuroactive peptides) to exposure to the enteric nervous system (ENS) [128, 131]. This leads to the release of inflammatory cytokines and the activation of vagus nerve and spinal afferent neurons that have been linked to psychiatric disorders such as depression and autism [54,132,133]. Studies suggest the protective role of probiotic bacteria to restore the increased intestinal barrier permeability by promoting the tight junctions between epithelial cells and reducing the permeability. Therefore, in summary, probiotics can influence the gut-brain axis and normalize the altered CNS functions through one or combination of above discussed mechanisms.

HPA: hypothalamic-pituitary-adrenal axis, CORT: corti-costeroid ACTH: adrenocorticotropic BDNF: brain-derived neurotrophic factor (BDNF), c-Fos, γ-aminobutyric acid (GABA), 5 hydroxytryptamine (5-HT), DA: dopamine, SCFAs: short-chain fatty acids

5. FUTURE CHALLENGES

Implications of brain-gut communication in the pathogenesis of psychiatric disorders indicate a possible role of strengthening human microbiota by delivering probiotics as a newer therapeutic option. The use of probiotics in the treatment of neurologic diseases as a routine additive therapy is surrounded with few issues.

From the animal and human studies, it was clear that dose of probiotic should be more than one million per day as most studies used 10^9 and 10^{10} CFU in animals and 10^9 CFU in humans. Also, the probiotic has to be taken over a lengthened time period which is from 2 weeks in animals and 4 weeks in humans or more to show a positive effect on the working of the brain in different mental ailments. However, studies related to the optimization of different formulations, use of targeted drug delivery vehicles, dosage regimen and timings, for each specific neurologic disease, still have to be focused [134].

Another aspect that needs future studies is the optimization of dosage and dosage timings among different set of population esp. depending on age (children, elderly, young) and other underlying conditions (diabetics, liver disorder, obese, cancer patients, pregnant women *etc*.) [135].

Since a vast array of neurological disorders have been identified to date that ranges from neurodegenerative defects, psychiatric disorders, post-trauma related disorders. Studies to evaluate the optimal probiotic mixture (single strain or multiple strain cocktail) for each specific disorder and set of the patient population needs future work. Also, the ability of each strain and commercialized product to remain viable in adequate numbers with high bio-availability at the target site needs consideration [136].

Another most important aspect is the safety and tolerability of probiotic strain administration with special focus on children, elderly, pregnant women *etc*. There have been two cases of Lactobacillus sepsis reported in newborns. Similarly, a case of sepsis was reported in child suffering from cerebral

palsy, mental retardation, and a seizure disorder [130, 131]. Similarly, Trinchieri *et al*. [132] reported that variability during the final manufacturing of probiotics is of major concern for efficacy and safety, especially in individuals affected by serious conditions such as Human Immunodeficiency Virus (HIV), Inflammatory Bowel Disease (IBD), or cancer. This warrant detailed study into the safety aspects of probiotic strain administered, its stability, its dose tolerability and related adverse reactions on the target population *etc*.

CONCLUSION

The present article has discussed the importance of our gut flora in mental health, which is directly linked to our overall health and happiness. By improving the quality of gut flora through regular intake of probiotic rich foods and dietary modifications, one can ensure a much calmer and happy state of mind. Evidence studies also indicate the significant role that probiotics play in brain homeostasis and the need for boosting gut health by regular consumption of probiotics bacteria. Thus, it is highly beneficial and recommended to consume probiotic rich diet and wherever recommended probiotic supplements for boosting brain and body – the key to sound mental health and well being. The potential usefulness of probiotics in preventing or treating neurologic diseases is becoming a topic of great interest. However, studies related to the formulation, dosage regimen for each specific neurologic disease, still have to be focused upon. Also, trials to evaluate the safety, tolerability in patients with neurologic diseases should be considered.

LIST OF ABBREVIATIONS

CNS	=	Central nervous system
HPA	=	Hypothalamic-pituitary-adrenal axis,
CORT	=	Corticosteroid
ACTH	=	Adrenocorticotropic
BDNF	=	Brain-derived neurotrophic factor
GABA	=	γ-aminobutyric acid
5-HT	=	5 hydroxytryptamine
DA	=	Dopamine
SCFAs	=	Short-chain fatty acids

AUTHORS' CONTRIBUTIONS

SK and VS conceptualized the idea and drafted the manuscript. All authors reviewed and approved the final draft.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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