

**A SEMINAR PAPER
ON
PSYCHOBOTICS: THE NEXT GENERATION PROBIOTIC FOR MENTAL HEALTH**



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A SEMINAR PAPER

ON

PSYCHOBOTICS: THE NEXT GENERATION PROBIOTIC FOR MENTAL HEALTH

ABSTRACT

Psychobiotics are a group of probiotics or groups of live bacteria which mainly affect the central nervous system (CNS) and its related functions and their behaviors which are regulated by the gut-brain-axis (GBA) through various pathways like as immune, humoral, neural, and metabolic pathways which improve the gastrointestinal (GI) function as well as the antidepressant and anxiolytic capacity of brain. There are many common gram-positive bacteria which are commonly used as psychobiotics. The major source of these bacteria is fermented dairy food products as well as other products. The application of psychobiotics has led a new field of researchers which focus on a new area in neuroscience and mental health. In the past few years, some of psychobiotics strains were reported to inhibit inflammation and decreased cortisol levels, which result in an amelioration of the symptoms of disturbed mental health like anxiety and depression. This psychobiotics are very effective in improving several neurodegenerative as well as neurodevelopmental disorders also. But the evidence for the effects of psychobiotics on mental and neurological conditions are remains limited in research field yet. Some animal and human studies are found but they are not sufficient and human research on psychobiotics is limited also. So, studies of psychobiotics are needed to increase in order to know their effectiveness and mechanism as treatments for various nervous as well as psychiatric disorders in the future. This paper reviews the beneficial properties of psychobacteria, their mechanism of action in brain and use of this bacteria in several mental and psychological disorder.

Keywords: Mental health; Gut-Brain Axis; Neurotransmitter, Anti-inflammatory; anti-depressive

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Chapter I

INTRODUCTIONS

1.1 Background

Our human gut contains various beneficial microorganisms, which is almost 100 times greater than the cells number of our body. This gut microbacteria plays various important roles in physiological processes, including immunomodulation, energy balance and activation of the enteric nervous system. Our microbial profile sometimes controlled by several factors like as their diet, genetics, sex, and age. This microbiota also plays critical roles in human health specially the dysbacteriosis of the gut microbiota is strongly correlated to various diseases of the central nervous system (CNS). Besides mental health is an emerging issue now and various researches are developed to improve our mental health. People are facing depression, bad mood, anxiety like mental issues and today it become more dangerous. There are many antidepressant drugs but various side effects are involved so that psychobiotics which posses very small or no side effects can be a great treatment for mental health issues. Besides there are various sources which can easily used by mental disease patients. Studied found that there is a strong relationship between psychobacteria and mental health and our emotional state is also impacted by the function of probiotics in gut. So that lower *Bifidobacterium* or *Lactobacillus* counts were noticed today for some major depressive disorder. Besides this other studied found that microbes can also regulate serotonin secretion in gut enterochromaffin cells (Yano *et al.*, 2015). The gut microbiota connects the nervous system through several pathways. So that the study of psychobiotics are utmost importance to know their potential, particularly in psychiatric and mental disorders.

Objectives:

After completing this article, readers will be able:

- To know the properties of psychobiotics & the relationship between psychobiotics & mental health
- To know the mechanism of action & highlight the beneficial effects & use of psychobiotics in mental health

Chapter II

METHODOLOGY

This seminar paper is completely a review paper. Any scientific works requires a close understanding of the subject matter. This paper mainly depends on various secondary data. Many published reports and data from different journals are mainly supported in providing information in this paper. So that no specific method has been followed in preparing this paper. All are collected by browsing internet like google, googleschooler, Pubmed and also studying comprehensively various articles published in different journals, books, proceedings, dissertation available in the libraries of BSMRAU and personal communication. The author also like to express her deepest gratitude to her major professor and course instructors for their effective scholastic guidance, important suggestions to create this manuscript. All the information collected from the secondary sources which are arranged here systematically and chronologically to enrich this paper.

Chapter III

REVIEW OF MAJOR FINDINGS AND DISCUSSION

3.1 Evolution of psychobiotics

The use of probiotic bacteria starts since the ancient times by human after the civilization of Egypt and Middle East. For extending shelf life of food they use fermentation process. In 1907, the effects of these microorganisms in health were discovered by Ely Metchnikoff, shown the higher longevity of Bulgarian farmers by the consumption of fermented dairy products. In 1953, for the first time the word “probiotics” was used refer to “essential active substances for the healthy development of life” (Gasbarrini G, *et al.*, 2016). After many years, new definitions of probiotics were proposed, but the official concept of probiotics was formulated in the year of 2001, when a panel of specialists of Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) defined probiotics as “live microorganism which, when administered in adequate amounts, confer a health benefit on the host”. Psychobiotics is a recent term use in the field of probiotics which have many health benefits. It is defined as; psychobiotics as those living organisms, upon sufficient ingestion produces a health benefit to patients with psychiatric illnesses. So that, the term “psychobiotics” designates it a novel class of probiotics, which has various applications in psychiatric medicine (Dinan *et al.*, 2013).

3.2 Psychobacterial species

3.2.1 Characteristics of psychobiotics:

- Prevent stress-induced alterations to overall intestinal microbiota
- Reduction of amine or uremic toxin burden
- Limitation of inflammatory cytokine production
- Direct protection of the intestinal barrier
- Limitation of carbohydrate malabsorption
- Influence on local and systemic antioxidant status
- Improvement of nutritional status,
- Indirect influence on neurotransmitter or neuropeptide production

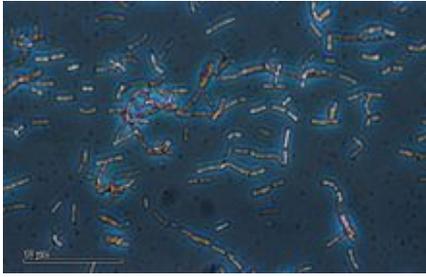


Fig. 1. *Lactobacillus acidophilus*



Fig. 2. *Lactobacillus plantarum*

Source: (J. Reisching, 2014 ; M. Kleerebezem *et al.*, 2003)

3.2.2 Common psychobacterial species

Now a day's several species of bacteria have been using as probiotic psychobiotic. Among them the species belong to the genus *Lactobacillus* and *Bifidobacterium* are widely used for probiotics treatment in the field of mental health as shown in Table 1. This probiotic psychobacteria could be used through various fermented dairy product or sometimes through capsules form various drug industries. The bacterial strains used as psychobiotics have been displayed in Fig. 3. Most of the strains belong to the species *Lactobacillus plantarum* (29%) followed by *Lactobacillus rhamnosus* (27%) and *Bifidobacterium adolescentis* (21%).

Table 1. List of common psychobacteria used in mental health treatment

Serial No.	Species name
1.	<i>Lactobacillus helveticus</i>
2.	<i>Lactobacillus casei</i>
3.	<i>Lactobacillus plantarum</i>
4.	<i>Lactobacillus acidophilus</i>
5.	<i>Lactobacillus bulgaricus</i>
6.	<i>Bifidobacterium breve</i>
7.	<i>Bifidobacterium infantis</i>
8.	<i>Lactobacillus rhamnosus</i>
9.	<i>Lactobacillus gasseri</i>
10.	<i>Bifidobacterium longum</i>

Source: (Bambury *et al.*, 2018)

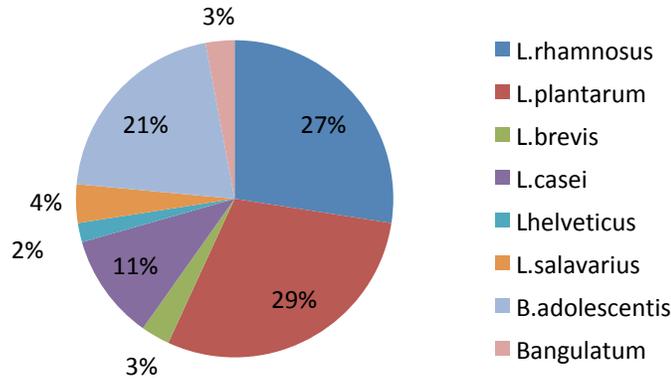


Fig. 3. Percentage of bacterial strain used as psychobiotics

Source: (Yunes *et al.*, 2016)

However, it is noteworthy to mention that some other intestinal microbial species such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Escherichia*, *Bacillus*, *Saccharomyces*, *Candida*, *Streptococcus* and *Enterococcus* have been reported to produce neurotransmitters such as serotonin, norepinephrine and gamma-aminobutyric acid which are associated with the upregulate the mental health. These bacteria have also documented to modulate the expression of neurochemical receptors such as endocannabinoid receptors and act on the postulated brain-gut axis which results in psychotropic effects like antidepressant and anxiolytic.

3.3 Relation of psychobiotics to mental health

The mental health is considered as an emerging issue and consequently various researches are ongoing on how to develop our mental health. Beside our physical health, mental health is also very important issue. A good mental health represents a status of complete mental, psychological well-being. The diversified field of human microbiome research, it has indicated that our gut microbiota may can play an important role in influencing brain development, behavior, and mood in humans (Mayer *et al.* 2014; Tillisch *et al.* 2013). It has been also showed that the psychobiotics have the psychotropic effects on several cases of mental disorder such as depression, anxiety and stress. Reports from animal studies suggest that gut microbiota have interaction both with the enteric nervous system as well as central nervous system through various pathways like neural, neuroendocrine, neuroimmune and humoral. In Table 2, the

bacterial strains have been grouped depending on the mental conditions for which they are reported.

Table 2. Psychobacterial strain in various mental conditions

Anxiety	Depression	Stress
<i>L. fermentum</i> NS9	<i>L. acidophilus</i>	<i>L. casei</i> Shirota
<i>L. caseishirota</i>	<i>L. acidophilus</i> W37	<i>L. helveticus</i>
<i>L. rhamnosus</i> JB1	<i>L. casei</i> W56	<i>L. helveticus</i> R0052
<i>L. helveticus</i> ROO51	<i>L. gasseri</i> OLL2809	<i>L. plantarum</i> PS128
<i>B. brevis</i> 1205	<i>L. helveticus</i>	<i>L. rhamnosus</i>
<i>B. infantis</i>	<i>B. infantis</i>	<i>B. infantis</i>
<i>B. longum</i> 1714	<i>B. bifidum</i>	<i>B. longum</i> R0175
<i>B. longum</i> NCC3001	<i>B. bifidum</i> W23	
<i>B. longum</i> R0175	<i>B. lactis</i> W52	
	<i>B. longum</i> R0175	

Source: (Misra *et al.*, 2019)

3.4 Food as a source of neurotransmitter producer

There is a relationship between fermented dairy products and the growth of beneficial intestinal microbes. Fermented dairy products (yogurt, cheese etc.) can be a good source of psychobacteria which possess some neurotransmitters, short chain fatty acid, protein molecules and other molecules which act as influencers in maintaining good mood. Among them studied shown that red rice treated yogurt have highest GABA content found.

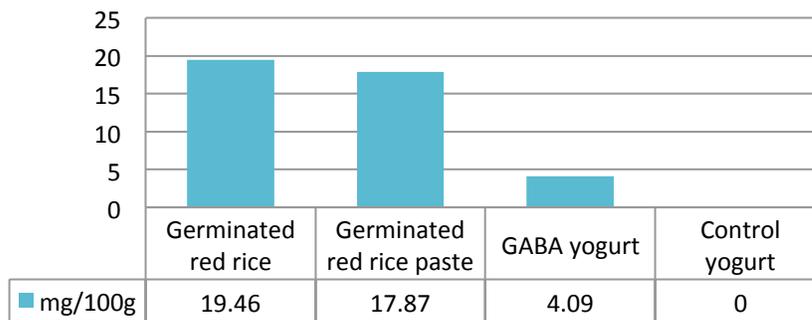


Fig. 4. Amount of GABA (Gamma Amino Butyric Acid) produced by rice treated yogurt

Source: (Anawachkul *et al.*, 2009)

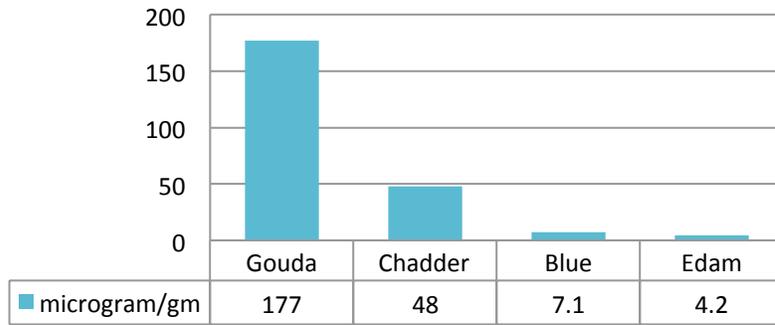


Fig. 5. Amount of GABA (Gamma Amino Butyric Acid) produced by different types of cheeses

Source: (M. Nomura *et al.*, 1998)

In recent studies, it is indicated that (non-dairy) fermented foods and herbs can also influence the intestinal microbiota. They are both equally important because they may be an influence on longer-term gut-brain communication. Besides various studies shown that some common dietary polyphenols which after fermentation are able to cause a beneficial increase in microbial growth (Selhub *et al.*, 2014). Such as isomaltoligosaccharides which are found in traditional foods like honey, sake, miso, and soy sauce, fermented cabbage like kimchi, and fermented fish oil, fiber-rich components of traditional diets like soygerm, wheat germ, rice bran, or breads. They have a beneficial effect in promoting the growth of *Bifidobacteria* and *Lactobacillus* spp (Goffin *et al.*, 2011; Han *et al.*, 2012; Selhub *et al.*, 2014).

3.5 Gut microbiota-brain axis in mental health

3.5.1 Mechanism of action

Gut microbiota are commonly referred to as psychobacteria which have several effects on the brain. It affects the brain through the nervous system by the gut-brain's neuroanatomical pathway along with some other systems like the endocrine system, immune system and metabolic system. This bi-directional communication between the gut and the brain is called the Gut-Brain axis. The gut microbiota-brain axis can communicate through several possible routes. Although the exact mechanism of the gut microbiota-brain axis has not yet been fully clarified, evidence from animal and human studies indicates the possible communication routes and mechanism of action as presented in Fig. 6.

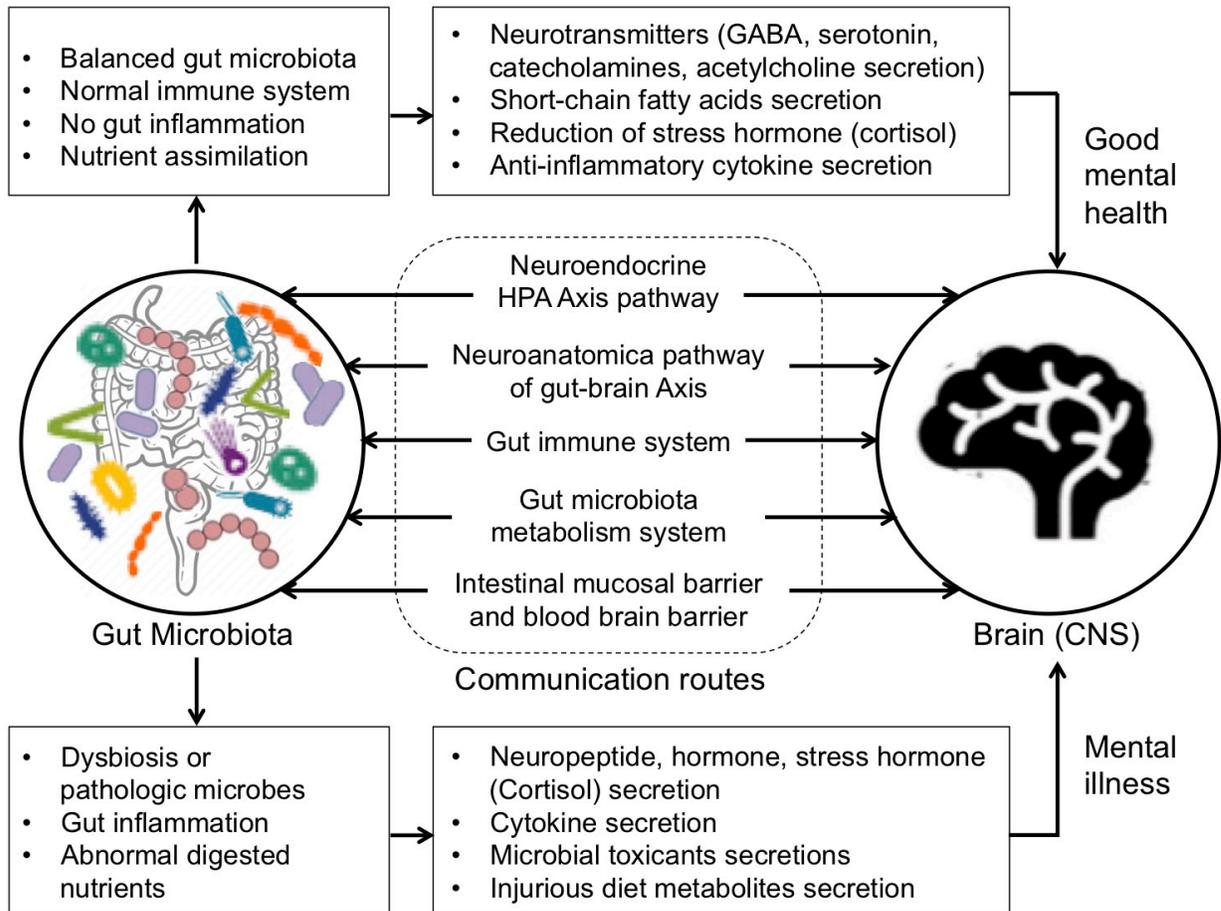


Fig. 6. Possible communication routes and mechanism of action of Gut-Brain Axis

Source: (Misra *et al.*, 2019)

01. Firstly, the enteric nervous system as well as vagus nerves connects the intestine with the central nervous system. Psychobacteria produce neurotransmitters or neuro-active molecules from enterocytes under control of gut microbes which influence the neural signaling of this gut-brain axis (Schmid *et al.*, 2015). When the concentration of neurotransmitters increases within the gut, it can decrease the plasma tryptophan concentrations which can triggers the gut lining cells to release molecules to the brain which can improve mental illness (Desbonnet *et al.*, 2008; Lyte 2011; Akkashah *et al.*, 2016). The various neurotransmitters produced by the different

genus of bacteria have been illustrated in Table 3. One of the important neurotransmitter is Gamma-aminobutyric acid (GABA) which is associated with anxiety, stress and fear. The production of GABA by various strains of psychobacteria is shown in Table 4. The highest amount of GABA is produced by *B. adolescentis* followed by *B. angulatum*. However, the well-known probiotic *Lactobacillus* strains produce less amount of GABA as compared to *Bifidobacterium* (Table 4.)

Table 3. Neurotransmitters produced by psychobacteria

Types of bacteria	Neurotransmitters produced
<i>Bacillus</i>	Dopamine, norepinephrine
<i>Bifidobacterium</i>	Gamma-aminobutyric acid (GABA)
<i>Enterococcus</i>	Serotonin
<i>Escherichia</i>	Norepinephrine, serotonin
<i>Lactobacillus</i>	Acetylcholine, GABA
<i>Streptococcus</i>	Serotonin

(Source: T.D. Dinan *et al.*, 2015)

Table 4. Amount of GABA produced by various strains of psychobacteria

Species	Strains	GABA (mg/L)
<i>L. plantarum</i>	29st, 50/2, k13, 75sk, 14/4, 36st, 9/1A, 106zv, 38/1	< 50
	46sk, 3/1, 7/1, 52/1, CS396, K9L, 50st3, 43/3, 119, 43/2, 56/1	51-100
	8-PA-3, 46k, 42/2, 191g, 57/1	101-150
<i>L. brevis</i>	47st, 52st	50-100
	15f	675
<i>B. adolescentis</i>	56, 174, 191, 104, 76, S11	<900
	108, 282, 48-2, 110	901-3000
<i>B. angulatum</i>	334-1, 212, GT102	2616-3459

Source: (Yunes *et al.*, 2016)

02. Some Short-chain fatty acids (SCFAs) like as butyrate, propionate, and acetate production which are also essential metabolic products of gut microbial activity. The other possibility of the mode of functioning of psychobiotics on the gut-brain axis can be through the SCFAs exerting central effects through G-protein–coupled receptors, although such receptors are sparsely concentrated in the brain. It is also likely that they act as epigenetic modulators through histone deacetylases (Stilling *et al.* 2014).

03. The third way that psychobiotics can act on the brain is by exerting effects on the body's stress response system, which involves the brain and the adrenal glands. This system known as the hypothalamic-pituitary-adrenal (HPA) axis. When HPA-axis dysfunction occurs, there is a disturbance of production and functions of stress-related hormones. This may play a central role in causing mood disorders as well as cognitive problems.

04. Several other studies have hypothesized that psychobiotic can act on the brain in the capacity of anti-inflammatory actions. Several chronic exposures which increase inflammatory cytokines and persistent alterations in neurotransmitter systems can cause neuropsychiatric disorders and depression. Besides inflammatory cytokines may play as mediators of both environmental such as childhood trauma, obesity, stress, and poor sleep as well as genetic functional gene polymorphisms also factors that have a role in the occurrence of depression (Fig. 6).

3.5.2 In vivo evaluation of psychobiotics effects on mental health

The emerging field of human microbiome research has indicated that gut microbiota may also play an important role in influencing brain development, behavior, and mood in humans (Mayer *et al.* 2014; Tillisch *et al.* 2013). In order to evaluate these effects, several in vivo trials including human and animals were performed.

3.5.2.1 Animal study

Some of the probiotics strains considered as psychobiotics were used for animal studies. As shown in the Table 5, administration of *Lactobacillus plantarum* PS128 can reduce anxiety and depression-like behaviors of mice and can also decrease inflammation and corticosterone levels. The single strain *Lactobacillus helveticus* NS8 administration can reduce anxiety, depression and cognitive dysfunction. Moreover, *L. helveticus* NS8 is also reported to increase the serotonin, nor epinephrine (NE) and brain-derived neurotrophic factor (BDNF) levels in the hippocampus. The single strain of *B. longum* 1714 can decrease the stress, depression and anxiety behaviors (Savignac *et al.*, 2014). The *Lactobacillus rhamnosus* (JB-1) can decrease anxiety and

depression. *Bifidobacterium longum* NCC3001 has been proved to be effective on treating anxiety. In addition, administration of signal strain of *Bacterium infantis* 35624 is also reported to be effective to modulate depression-like behaviors (Desbonnet *et al.*, 2010).

Table 5. Cases of animal study

Species used	Model	Observations
<i>L. Plantarum</i>	Germ free mice(GFM)	<ul style="list-style-type: none"> • Reduce anxiety • Increase locomotion activities
<i>L. Brevis</i>	Innately anxious BALB/c male mice	<ul style="list-style-type: none"> • Reduce anxiety and depression
<i>L. rhamnosus</i>	Normal/healthy BALB/c male mice	<ul style="list-style-type: none"> • Increase memory • Reduce depression & anxiety
<i>L. paracasei</i>	Depressed male mice	<ul style="list-style-type: none"> • Reduce depression & anxiety • Increase anhedonia

Source: (Dinan *et al.*, 2019)

3.5.2.2 Human study

In addition to these promising animal studies, some research has also found positive effects of probiotics on mental health in humans. Some healthy volunteers who were administered *Bifidobacterium longum* 1714 strain for duration of 4 weeks and finally they shown reduced stress and also improved their memory condition (Allen *et al.*, 2016). In a randomized trial on petrochemical worker investigated the positive effects of probiotic yogurt containing *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 and a probiotic capsules containing *Lactobacillus casei*, *L.acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum* and *Streptococcus thermophiles* (Mohammadi *et al.*, 2016) .

Table 6. Cases of human studies

Study design	Microbes used	Duration of study	Observations	References
Human	A mixute of <i>Bifidobacterium bifidum</i> W23, <i>Bifidobacterium lactis</i> W52, <i>Lactobacillus acidophilus</i> W37, <i>Lactobacillus brevis</i> W63, <i>Lactobacillus casei</i> W56, <i>Lactobacillus salivarius</i> W24, and <i>Lactococcus lactis</i> W19 and W58	4 weeks	Reduced rumination and aggressive cognition	Barrett <i>et al.</i> , 2012
Human	A mixture of <i>L. helveticus</i> and <i>B. longum</i>	30 days	Less psychological distress	Messaoudi <i>et al.</i> , 2011
Human	A mixture of <i>Lactobacillus casei</i> Shirota	3 weeks	Improved mood	Benton <i>et al.</i> , 2007
Human	A mixture of <i>Bifidobacterium animalis</i> subsp. <i>Lactis</i> , <i>Streptococcus thermophilus</i> , <i>Lactobacillus bulgaricus</i> and <i>Lactococcus lactis</i> subsp. <i>Lactis</i>	4 weeks	Influenced brain activity	Tillisch <i>et al.</i> , 2013

Source: (Misra *et al.*, 2019)

3.5.2.3 Global trend of clinical trial on Brain-Gut Axis (BGA)

The outcomes of the clinical research on probiotics in BGA are very heterogeneous depending on the mental disorder as well as the group of people studied. The Fig. 7 documented the outcomes of the different clinical trials among healthy population sick population. For instances, in the case of anxiety only one study showed no significant difference Vs placebo on healthy population whereas the study number was higher those showed significant differences on healthy population. The heterogeneity occurs due to variety of people and strains involved. The

substantial numbers (66) of registered clinical studies on psychobiotics are ongoing as shown in the Fig. 8. The highest number of studies has been targeting the stress and anxiety disorder followed by cognition and brain, ADHD and autism etc.

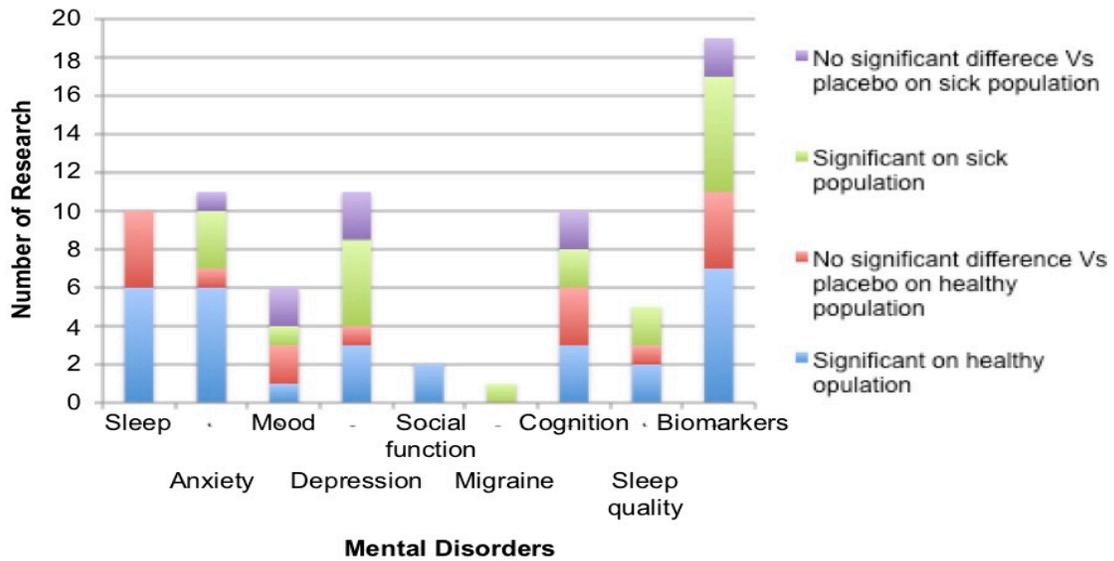


Fig. 7. Overview of clinical outcomes of psychobiotic on Brain-Gut Axis

Source: (WHO Database, January 2012- January 2019)

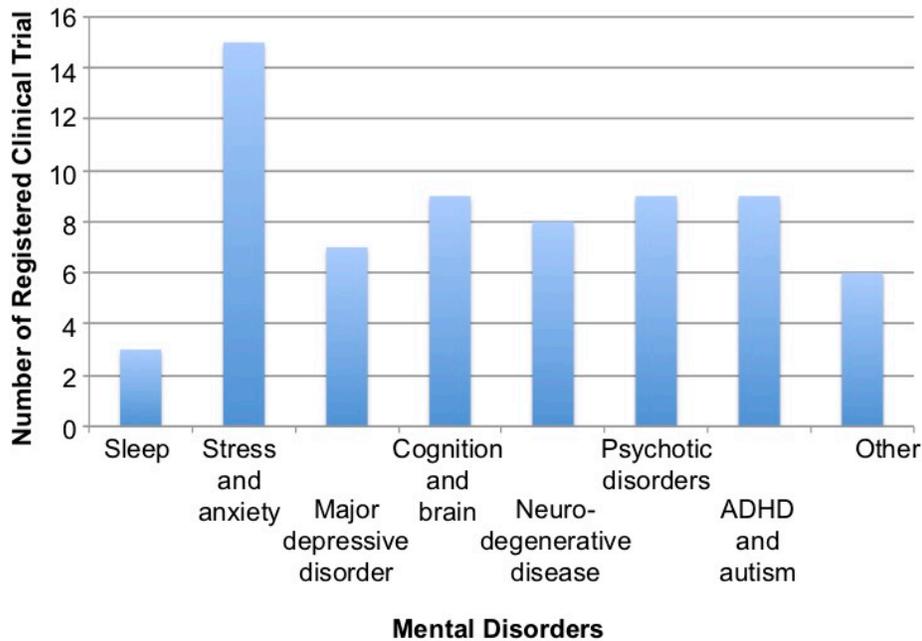


Fig. 8. Registered clinical studies on psychobiotics

Source: (WHO, 2017 – Mid 2019)

3.5.3 Combination of psychobiotics

Sometimes combination of various strains of psychobiotics gives more good results than using single strain. There are five combination pattern of psychobiotics have been reported and reviewed by Misra 2019 (Table 7). For example the combination number 3 in Table 7 was tested on healthy female volunteers for a period of 4 weeks. The volunteers consumed fermented milk product containing a mixture of probiotics including *Bifidobacterium animalis subsp. Lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and *Lactococcus lactis subsp.Lactis* and the results showed that probiotic consumption influenced their brain activity in emotional centers (Tillisch *et al.*, 2013). In addition, another study shown that healthy peoples who were given a mixture of probiotics including *L. helveticus* and *B. longum*, for a period of 30 days, they results less psychological distress after measured by various instruments (Messaoudi *et al.*, 2011).

Table 7. Effective combination pattern of psychobiotics

1. <i>Lactobacillus curvatus</i> and <i>Lactobacillus plantarum</i>
2. <i>Lactobacillus helveticus</i> and <i>Bifidobacterium longum</i>
3. <i>Bifidobacterium animalis</i> subsp. <i>Lactis</i> , <i>Streptococcus thermophiles</i> , <i>Lactobacillus bulgaricus</i> and <i>Lactococcus lactis</i> subsp. <i>Lactis</i>
4. <i>Bifidobacterium infantis</i> and <i>Lactobacillus salivarius</i>
5. <i>L. acidophilus</i> , <i>B. lactis</i> and <i>L. fermentum</i>

Source: (Misra *et al.*, 2019)

Another studied shown that consumption of probiotic yogurt as well as multispecies probiotic capsule for a period of 6 weeks can results beneficial effects on mental health parameters in petrochemical workers (Mohammadi *et al.*, 2015). The following table shows the psychobacteria use for combined treatment.

Table 8. Psychobacteria used for combined treatment

Depression & Stress	Depression & Anxiety	Stress & Anxiety
<i>B. breve</i> 1205	<i>L. helveticus</i>	<i>B. bifidum</i> W23
<i>B. longum</i> 1714	<i>L. rhamnosus</i>	<i>B. lactis</i> W52
<i>B. longum</i> NCC3001		<i>L. acidophilus</i> W37
<i>L. fermentum</i> NS9		<i>L. brevis</i> W63
		<i>L. casei</i> W56
		<i>L. helveticus</i> NS8
		<i>L. salivarius</i> W24
		<i>L. lactis</i> W19L.

Source: (Misra *et al.*, 2019)

3.6 Increase of psychobiotics in gut (food pyramid)

It is now proved that many of our mental illness starts with gut. Gut is not only the cause of all mental illness but it can lead illness like depression, anxiety, mood disturbance. The psychobacteria can improve the mood by produce serotonin or dopamine. The junk food can make us happier for a small period of time but intake of psychobiotics can improve our gut

environment and lifting our mood. So the first step must be the modification of diet for giving support of the psychobiotics. The following Fig. 8 of food pyramid can completely shows the food we need for psychobiotic supplements. Green vegetables, fruits are daily requirement



Fig. 9. The food pyramid of psychobiotic

Milk and milk products, eggs must have to take weekly as well as fish, meat, and sea foods are often taken. Besides those foods some common habits like as avoiding sugar and intake of fermented food, vegetables, fish, and high fiber vegetables can improve gut bacteria for our good mental health condition.

Chapter IV

CONCLUSIONS

Psychobiotics are probiotics which have various beneficial health effects including nervous system activities. This probiotics can connects with our brain through various pathways and enhance the brain activities as well as improve mental condition. Various gut bacteria as well as other bacteria can be a good source of psychobiotics and it become an excellent treatment for the mentally disturb people for a wide range of illness.

For various physiological and chemical stressors microbial dysbiosis occur and our brain get negative feedback and which causes production of several stress hormones where psychobacteria produce various neurotransmitters and other molecules which influence the brain to reduce the production of stress hormone. Besides this psychobiotics posses less side effect then others antidepressant drugs. Though the psychobiotic treatment is costly but it alleviated the life quality of mentally ill peoples.

The beneficial effect of psychobiotic and its use in mental health is the main focus in this review paper because it has the potential capability to improve our mental condition which is very much important for today's perspective. And it is now proved that psychobiotics are naturally adapted to our intestinal environment which naturally modulated the Gut-Brain-Axis. This psychobiotics in a food form are increasing their popularities, hence the nonconventional antidepressive treatment shows a promising future in the field of neuroscience. Further researches are recommended to affirm that psychobiotics can be an excellent treatment for mental health.

Chapter V

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