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Exploring the promise of psychobiotics: Bridging gut microbiota and mental health for a flourishing society

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ABSTRACT

Mental health problems have become one of the major issues worldwide. People of every age group and gender are facing psychological issues. Conventional medicines are not reliable due to their adverse effects like altered sleeping pattern, addiction and health problems throughout the entire body. Psychobiotics is a new class of probiotics that is serving a wide range of applications in psychological health. Psychobiotic refers to the biological formulation which when consumed in right amount, confers psychological benefits. A lot of studies have supported the function of gut microbiota in mood cognition and controlling anxiety. The mechanism of action of psychobiotics has not been completely investigated. However, it may confer benefits by modulating hypothalamic-pituitary-adrenal (HPA) axis, by directly influencing immune system and through production of various neurotransmitters and neurohormones like proteins and short fatty acids chains. This review highlights the potential of different bacterial strains in human and animal trials. It latter also covers various psychobiotics formulations marketed by different companies. In addition to this, we also tried to cover the various hurdles in psychobiotic research that need to be addressed in the future to build a prosperous society.

1. Introduction

Mental health problems are highly prevalent among the countries worldwide. The occurrence of several mental diseases depends upon gender and age. Anxiety and depression are the most prevalent illness which imbalances the mental functioning of all the individuals. Suicide is a global issue affecting people and their families worldwide irrespective of their age. It is a leading cause of death among adolescents. On an average, one in eight people is facing psychological issue globally. Mental health conditions are undertreated and 71 % of the affected people does not get any medical attention. Lack of resources is also a major factor responsible for prevailing conditions. Only 2 % of the budget is given for mental health (Fig. 1) [1]. Depression, stress and major depressive disorder are multifaceted diseases characterized by significant impairments in global functioning, anorexia, and serious medical multimorbidities. Around 20 % of the population are affected by MDD during once in their lifetime [2,3]. There are numerous interventions available to treat these problems but these solutions, usually take a while to work, causing emotional instability, altered sleeping pattern, addiction, and health problems throughout the entire body.

The human gut inhabits up to 10^{13}–10^{14} microorganisms which can range up to ten times of the eukaryotic cells in the body making it one of

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the most complex and abundant ecosystem [4]. The adult human gut microbiota is made up of 500–1000 different bacterial species [5]. A number of studies are being conducted on human microbiomes and their relationship to mental health which clearly states some unexplored connection between gut microbes and other aspects of physiology [6]. Research on animals has shown that gut bacteria interacts with both enteric nervous system and central nervous system (CNS) through humoral, neuroendocrine, neuroimmune, and neuronal connections, among other physiologic processes. Gut microbiota exhibits a vital role in neuroimmune modulation which results in developing signs and symptoms of various psychological disorders like depression, anxiety, autism spectrum disorders, Parkinson's disorder and Alzheimer's disorder [7]. The make-up of the microbial population inhabiting the gut directly affects the neuroimmune system; however, modern lifestyle factors like poor nutrition, stress, inactivity, and antibiotics in food and medicine can deplete these microorganisms, leading to emotional, mental, and physical instability. Lack of these advantageous microorganisms could have negative effects on health [8]. Beneficial microorganisms have been found in both human and animal studies to improve cognition and lower symptoms of depression, anxiety, and stress. These findings raise the possibility of a novel class of probiotics called "psychobiotics." Psychobiotics is a type of probiotics that is efficient in synthesizing and transporting neuroactive substances like γ-aminobutyric acid and serotonin that functions through the gut-brain axis [9]. They can also increase the amount of oxytocin (the "cuddle" hormone) and decrease the amount of cortisol (the "stress" hormone) (10,11]). γ-Aminobutyric Acid (GABA) and serotonin are primary neurotransmitters required for normal functioning of brain. They are produced by some strains of *Lactobacillus* spp. and *Bifidobacterium* spp., like *Bifidobacterium dentium, Lactobacillus plantarum* and *Lactobacillus brevis* (12, 13,14]. In addition, *Lactobacillus plantarum* and *Lactobacillus odontolyticus* synthesize acetylcholine which is a major inhibitory neurotransmitter in the brain which regulates different psychological and physiological functions [15]. This review highlights different psychobiotic strains, their modes of action and their impact on neuropsychological disorder. It also discusses the current market value and future perspectives related to psychobiotics.

2. Scope of the review

This review comprehensively highlights several key insights (as placed below) into the emerging field of psychobiotics, underscoring their potential therapeutic roles in mental health as compared to earlier published reviews [16–18].

2.1. Mechanistic understanding

The deep understanding of mechanisms of various psychobiotics, particularly their influence on the gut-brain axis, highlights the intricate biochemical pathways through which these microorganism's acts. This study can help in constructing more targeted medications by employing specific strains by regulating neurotransmitter levels, reduce inflammation and enhance gut health.

2.2. Mental health implications

The evidence supporting the role of psychobiotics in mental disorders is compelling, with studies demonstrating their potential to alleviate symptoms of anxiety, depression, and stress-related disorders. Psychobiotics could act as complementary therapies, offering a new option for patients who do not respond well to conventional medication.

2.3. Clinical trial advancements

The detailed and comprehensive review of clinical trials reveals promising results from various psychobiotic strains, indicating a growing body of evidence that supports their efficiency. The superior benefits of specific strains can be harnessed to develop personalized psychobiotic therapies.

2.4. Commercial landscape

This review covers the diverse range of commercially available psycobiotics along with their psychological benefits. This unique section illustrates the increasing interest in their application.

3. Mechanism of action of psychobiotics

The mechanism of action by which bacteria confers psychobiotic properties has not been thoroughly studied. However, it has been observed that these bacteria confer advantages through stimulation of immune responses or the enteric nervous system. They also influence the psychophysiological symptoms of stress and anxiety. The psychophysiological change may occur through three different mechanisms i.e., first by modulating hypothalamic-pituitary-adrenal (HPA) axis stress mechanism and lowering systemic inflammation; second, via affecting body immunity directly; third by production of various neurotransmitters like proteins, and short fatty acids chains (Fig. 2) [19].

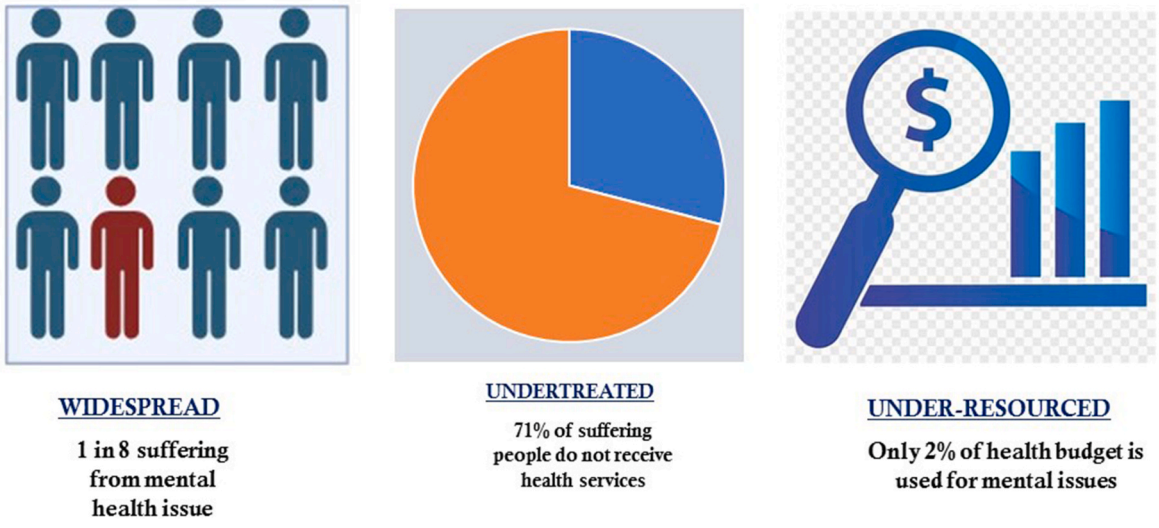

Fig. 1. Current scenario of world mental health [1].

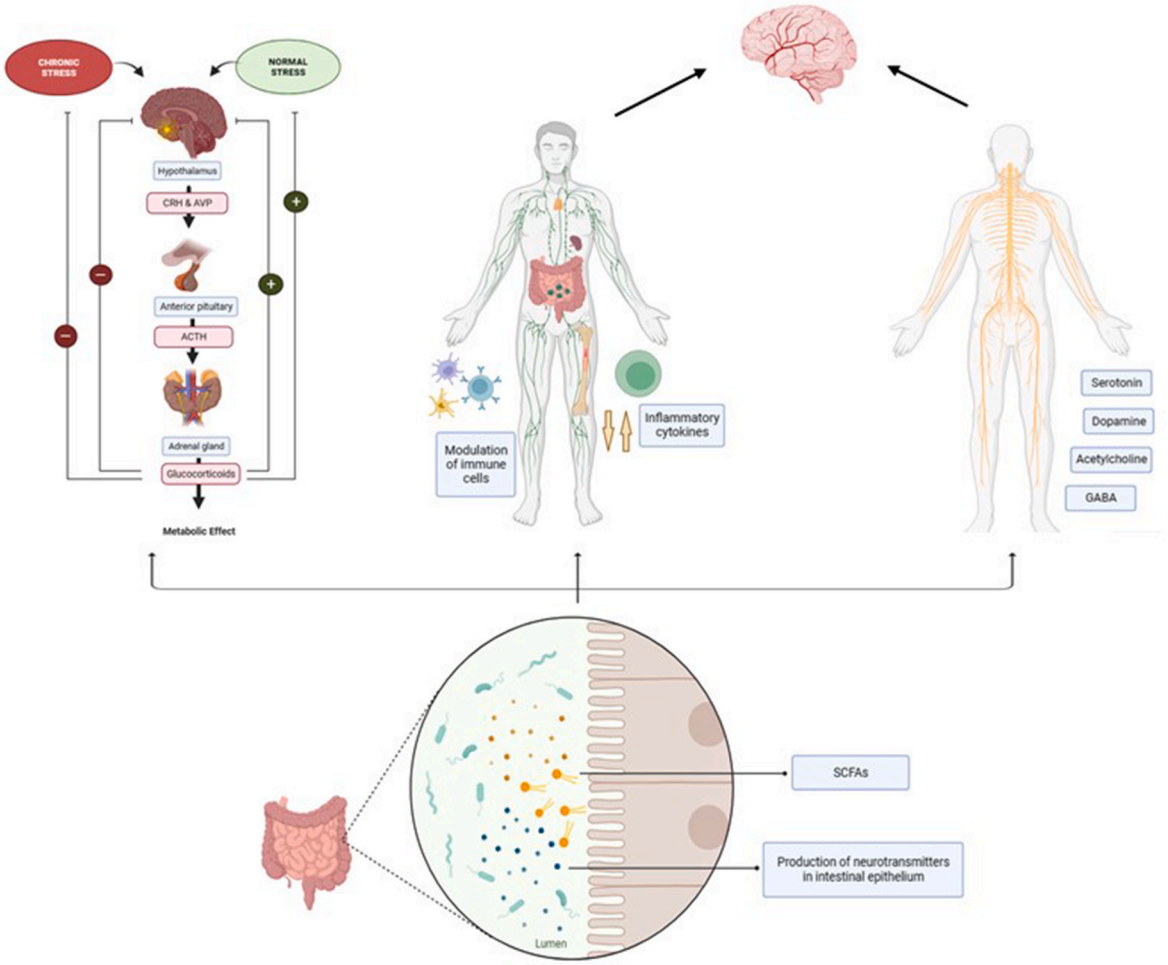

Fig. 2. Mechanisms involved in achieving psychoactive benefits through different microorganisms

3.1. Hypothalamus pituitary axis (HPA)

The HPA axis is the centre of neuroendocrine response system in humans which deals with different types of stress. It consists of hypothalamus, pituitary gland, and adrenal cortex in addition to some hormones, secreted factors and regulatory inputs [20]. The HPA axis is coordinating centre of the body which provides strength to cope with both internal and external stress factors through a series of hormonal changes. This process begins with the production of arginine vasopressin and corticotropin releasing hormone from paraventricular nuclear region of hypothalamus. Both the hormones, AVP and CRH acts on the anterior pituitary of the brain resulting in release of pituitary adrenocorticotropin (ACTH) in blood [21–24]. Then, ACTH stimulates the production of glucocorticoids (GC) (cortisol in human, corticosterone in rodents) from the adrenal cortex. These hormones play important functions throughout the body by maintaining homeostasis and mobilizing energy resources to deal with different types of stress [25]. Cortisol is over-synthesized under conditions of chronic anxiety but it fails to acquire its anti-inflammatory potential. As a consequence, the negative feedback mechanism of cortisol on the HPA axis is inhibited, causing hypercortisolemia [26]. The overproduction of glucocorticoids is the cause of various negative impacts on the body like immune inactivation, memory impairment, mood swings, threat sensitivity and other cognitive functions. Various recent findings support the idea of strong two-way communication link between gut microbiota and neuroendocrine system. Early-stage gut colonization of microbial community has a major impact on both brain and behavior, as well as the stress response. It is evident from various studies that neuroendocrine abnormalities are directly related to changes in the intestinal permeability [27]. Liao et al. [28] studied the result of serving probiotic, *Lactobacillus paracasei* PS23, to maternal separation mice facing psychoactive issues like anxiety and depression. When heat-killed and live PS23 cells were given to MS animals, the behavior of the animals was improved. As compared to the negative control, there was a significant increase in exploratory inclinations and mobility of animals, indicating decreased levels of depression and anxiety ($P < 0.05$). In addition, mice given both live and heat-killed PS23 cells had decreased levels of corticosterone and increased quantity of the anti-inflammatory interleukin 10 (IL-10) in serum ($P < 0.05$). This highlight stress-mediated increase in immunomodulatory properties. Additionally, *Lactobacillus Plantarum* PS128 decreases anxiety and depression-like signs in mice exposed to pre-mature maternal-separation stress (postnatal day 2–24). There was reduction in blood corticosterone levels and increase in levels of dopamine and serotonin in prefrontal cortex [29]. *Lactiplantibacillus plantarum* has also been studied to confer psychoactive benefits via its effect on the HPA axis and levels of pro-inflammatory cytokines [30].

3.2. Immune response and inflammation

Psychoactive properties are also attained by the modulation of low-grade inflammation by lowering the amount of circulating pro-inflammatory cytokines. Pro-inflammatory cytokines also increase the permeability of the blood–brain barrier [31], providing way to infectious entities. Cytokines change the concentrations of several neurotransmitters like serotonin, dopamine, and glutamate that are involved in proper communications of brain [32]. They may get access to brain

via active update, stimulating production of pro-inflammatory substances like prostaglandins which further leads to inflammation [33]. Some studies have indicated a lymphatic drainage system serving the brain which increases the probability of interaction of cytokines with neural tissue. Enhanced levels of anti-inflammatory cytokines like interleukin-10 can also be considered a parallel mechanism to achieve psychobiotic-mediated decrease in inflammation. For instance, *Lactobacillus rhamnosus* GG have been shown to increase levels of interleukin-10 in humans. Psychobiotics may be preventing cytokines from reaching to the central nervous system by lowering the overall amount of pro-inflammatory cytokines, either directly or through enhancing anti-inflammatory cytokines. They also restore the permeability of the blood–brain barrier resulting due to inflammation [34–36]. Leclercq et al. [37] studied the impact of long-term dosage of antibiotic administration on the neurochemistry and behavior of rodents. They find out that the addition of antibiotics had a long-lasting effect on the composition of the gut microbiota, which in turn affected behavior, altered the blood-brain barrier's function, and increased cytokines secretion in the frontal cortex. These mice also exhibited significant aggression along with anxiety and impaired social behaviors. It must be noted that, in the same experiment, one test group was also provided with *Lactobacillus rhamnosus* JB-1, which resulted in the preventing various abnormalities discussed earlier.

3.3. Neurohormones and neurotransmitters

The gut microbiota can synthesize an array of neuroactive substances. Gut microbiota has been studied to synthesize numerous neurochemicals like acetylcholine, serotonin, gamma-aminobutyric acid (GABA), noradrenaline and dopamine that directly determine the brain functioning. Microbially synthesized long and short-chain fatty acids also possess neuroactive properties. Hence, the capability of some bacteria to synthesize and transport neurotransmitters and neuromodulators within the human gastrointestinal tract has been proposed as a novel approach to deal with neuropsychiatric issues [38].

3.3.1. Serotonin

Serotonin, also known as 5-HT or 5-hydroxytryptamine, is a neurotransmitter that is known for its ability to maintain mood and monitoring behavioral and biological processes of the body. It is also a main factor in psychological functions in the peripheral tissues and central nervous system (CNS) [39]. Antidepressants that act on nerve cells to stop 5-HT reabsorption are recommended as primary treatment for various psychiatric diseases like bipolar disorder, major depressive disorder, anxiety and post-traumatic stress disorder [40,41]. 5-HT is mainly present in the intestinal mucosa, 90%–95 % of serotonin is present in neurons of the enteric nervous system and enterochromaffin cells (ECs) of intestinal epithelium. Although the exact reason behind this location is not known, it might be linked to regular gut processes like absorption, transit and intestinal motility [42]. Gut microbiota has been studied to enhance 5-HT biosynthesis from ECs which is directly involved in gastrointestinal mobility and platelet functioning [43,44]. Li et al. [45] reported *Bifidobacterium longum* and *Lactobacillus rhamnosus* improved the chronic unpredictable mild stress (CUMS)-induced loss of weight and depressive-like behaviors to a certain extent. Rats supplemented with probiotics tended to have lower colonic 5-HT and higher 5-HT in the frontal brain and hippocampus. In a recent study, *Bifidobacterium dentium* has regulated the serotonergic levels and gut brain axis in mice which was accompanied with change in behavior of adults [46].

3.3.2. Dopamine and epinephrine

Dopamine (DA), norepinephrine (NE), and epinephrine (EP) are type of catecholamine (CA) neurotransmitters originated from tyrosine. They serve major roles in memory, learning, motor control and in stress response. By controlling the body's metabolism of lipids and carbs, they also have a significant impact on the cardiovascular system [47,48]. NE and DA acts as modulators of the prefrontal cortex which is involved in various body functions like taking decisions, attention, and inhibitory control. Dysfunctioning of the prefrontal cortex has been studied as a major reason of various psychiatric illnesses like drug addiction, schizophrenia, post-traumatic stress disorder (PTSD) and attention deficit hyperactivity disorder (ADHD) [49]. In research carried out by Liu et al. [50]; the 12-week treatment of *Lactobacillus plantarum* DR7 resulted in a reduction in levels of anxiety and stress in comparison of placebo group. It was associated with modifications in the brain's serotonin and dopamine-epinephrine neurotransmitter pathways. In another study, effect of *Lacticaseibacillus rhamnosus* 12L and *Lactiplantibacillus plantarum* 8PA3 was evaluated on the behavior of mice in a three-week study. Both tested strains were reported to produce serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), as well as dopamine, which was further metabolized into norepinephrine by *L. plantarum* 8PA3 and epinephrine by *L. rhamnosus* 12L [51].

3.3.3. GABA

GABA is a well-known inhibitory neurotransmitter which plays major role in controlling excitatory and inhibitory neurotransmission in the central nervous system. It is a non-proteinogenic amino acid. It regulates the intricate brain functioning such as synaptic plasticity, neuronal excitability, and cognitive functions [52–54]. GABA has also been synthesized by few intestinal bacteria that is linked with psychological conditions like depression and anxiety [55]. Human gut-inhabiting strains of *Lactobacillus brevis* and *Bifidobacterium dentium* have been investigated to be the major GABA producers among the tested strains [13]. GABA synthesized in gut reaches the central nervous system through GABA transporters located on the blood brain barrier [56]. According to Bravo et al., the feeding of *Lactobacillus rhamnosus* to mice changed the occurrence of GABA receptors in different areas of brain, leading to decreased levels of psychological symptoms [57]. It is still not clear whether the GABA produced from peripheral sources may pass the blood-brain barrier by active transport or through diffusion [58]. It has been investigated that *Lactobacillus brevis* CRL 2013 is capable of growing and synthesizing significant levels of GABA in MRS broth containing hexoses like glucose or fructose [59]. *Limosilactobacillus fermentum* and *Lactiplantibacillus pentosus* have also been studied as potential psychobiotics due to their ability to produce GABA [60]. *Limosilactobacillus reuteri* DSM 17938 has also been investigated to exhibit GABA production and anti-inflammation capability [61].

3.3.4. SCFA

SCFAs or small chain fatty acids are organic monocarboxylic acids having up to six carbons atoms. They are synthesized by gut microorganisms in large intestine via anaerobic fermentation of indigestible polysaccharides like the dietary fibers and resistant starch [62,63]. They mostly comprise of acetic acid (C2), propionic acid (C3), and butyric acid (C4) [64,65] in an estimated molar rate of 60:20:20, respectively [66]. Approximately 500–600 mmol of SCFAs are synthesized every day in the gut which mainly depends upon gut transit time, composition of microbiota and amount of fiber in the diet [67,68]. SCFAs plays various important roles in maintaining the epithelial barrier, proper functioning of the inflammatory response, immune system, lipid metabolism and adipose tissue at different levels. They also regulate host cellular metabolism [69]. Furthermore, by maintaining the integrity of the blood-brain barrier, neurotransmission regulation, controlling neurotrophic factor levels, and encouraging memory consolidation, SCFAs may have a direct impact on neural function. A number of studies highlights the major impact of SCFAs in gut-brain axis signalling [70]. According to research, patients with acute ischemic stroke who have low fecal levels of SCFAs have a higher chance of having poor functional outcomes after 90 days [71]. Zeng et al. [72] also reported a decrease in number of butyrate-producing bacteria and lower levels of fecal butyrate in individuals facing high risk of stroke. *Bifidobacterium longum*

1714TM has also been studied to lower the occurrence of stress, anxiety and depression like behaviors in mice [73,74]. In another study, *Bifidobacterium breve* 207-1 was reported to influence neurotransmitter and the HPA axis hormone levels via the microbiome-gut-brain axis. It also increased secretion of short chain fatty acids (SCFA) i. e., acetic and propionic acid [75].

4. Role of psychobiotics in mental disorders

4.1. Depression

Depression has become a major concern in the present scenario which affects a person both mentally and physically. It is often accompanied with other mental illnesses and loss of desire to live. It refers to a condition in which a person has a sense of low self-worth, pervasive guilt, difficulty experiencing emotions, and a reduced ability to find joy in life lasting for more than two weeks [76]. According to data from the WHO, depression impacts over 300 million individuals globally [77]. Recently, a number of studies have highlighted the change of gut microbiota in major depression disorders (MDD) patients [78–82]. Additionally, transferring fecal microbiota from depressed individuals into microbiota-deficient rodents led to the transmission of depressive traits [80], highlighting the important role of gut microbiota in the initiation of depression. With the increasing knowledge of microbiota-brain-gut axis, a number of study has reported mitigation of various psychological issues with probiotics [81]. In a study, chronically stressed C57BL/6J male mice were administered viable *Bifidobacterium breve* CCFM1025 for 5 weeks which resulted in decrease in depression and anxiety like behaviors. There was alleviation of hyperactive hypothalamic-pituitary-adrenal response, as well as inflammation. At the same time, gut microbial abnormalities caused by chronic stress were also restored and there was an increase in levels of SCFA and 5-HTP [83]. *Lactobacillus helveticus* has also been studied to deal with cognitive impairment, anxiety, and sadness. It has also boosted levels of BDNF, norepinephrine, and serotonin in the hippocampus, indicating its effectiveness in adjusting neurochemical pathways related to mood regulation [84]. In a 6-week study, seventy petrochemical workers were divided into three groups and given either probiotic yogurt containing *Bifidobacterium lactis* BB12 and *Lactobacillus acidophilus* LA5, or probiotic capsules containing *Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Lactobacillus acidophilus, Streptomyces thermophilus* and *Lactobacillus casei* or conventional/ordinary yogurt containing the starter cultures of *Streptococcus thermophilus* and *Lactobacillus bulgaricus*. The results demonstrated that consuming probiotic yogurt and probiotic capsule had a beneficial effect on general health questionnaire (GHQ) and depression anxiety and stress scale (DASS) scores. However, the group that received ordinary yogurt did not experience any significant improvement [85]. Administration of a new psychobiotic *Lactobacillus plantarum* PS128TM for 8-week, decreased stress, anxiety, and insomnia among IT specialists facing severe-stress [86]. The psychoactive properties of psychobiotics are further confirmed by a randomized controlled study conducted by Tian et al. [87] which reported improvements in both depressive and gastro-intestinal symptoms. Their study found significant reductions in depression scores among patients with major depressive disorder who were given multi-probiotics, compared to those who received a placebo, as measured by scales like the Hamilton Depression Rating, Montgomery-Asberg Depression Rating, and Brief Psychiatric Rating Scales. Additionally, probiotics markedly improved gastrointestinal function, as reported through self-assessments with the Gastrointestinal Symptom Rating Scale. These improvements are largely attributed to the modulation of the serotonergic system, which plays a key role in enhancing both brain and gut health.

4.2. Schizophrenia

Schizophrenia (SCZ) is a severe neurodevelopmental disorder that affects around 20 million people globally each year. The word “schizo” means split and “phrenia” refers to mind (Greek origin) which does not indicate the split personality disorder. It is a condition of disintegrated or scattered form of thoughts, emotions, and behavior. Schizophrenia affects individuals both socially and economically, causing severe impairment or weakening. It is marked by events of psychosis that can be either continuous or intermittent and includes positive, negative, and cognitive symptoms. Positive symptoms involve the excess expression of normal functions, such as delusions, hallucinations, disorganized speech, and catatonic behaviors. Negative symptoms reflect a reduction in normal functions, including lack of emotions and interest, limited speech, and aimlessness. Cognitive symptoms include confusion and poor verbal memory. Symptoms typically begin in early adolescence and can be accompanied by other psychotic disorders like depression and anxiety, complicating diagnosis. Current treatments focus on antipsychotics that target type 2 dopamine receptors, but these have largely failed to address issues related to attention and memory [88,89]. Antipsychotic medications act as the first line of defence against schizophrenia but the majority of patients didn’t response to treatment. Constipation is a major side-effect of this medicine which affects up to 60 % of people [90,91]. Recent studies have examined how gut microbiota variations in individuals with schizophrenia differ from the normal microbial diversity of healthy people. As compared to healthy guts, the ninety patients of medication-free schizophrenia harbors certain facultative anaerobes such as *Lactobacillus fermentum*, *Alkaliphilus oremlandii*, *Cronobacter sakazakii/turicensis*, and *Enterococcus faecium* in their gut. Notably, there was an increased presence of the phylum *Proteobacteria*, with a major richness of genera like *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella*, and *Methanobrevibacter*. Conversely, there was a reduction in genera such as *Coprococcus*, *Roseburia*, and *Blautia*. Additionally, metagenomic analysis of the normal gut microbiome has reported higher level of *Lactobacillaceae* during the early stages of disease development compared to healthy controls [92–94]. In a double-blind, placebo-controlled trial, the group of schizophrenia patients who were receiving risperidone with probiotic adjuvant therapy showed alleviation of clinical symptoms and reduced levels of IL-6 as compared to the group of patients with schizophrenia who received risperidone without probiotics as adjuvant therapy [95].

4.3. Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders affecting children and adolescents. Its prevalence has been steadily rising over the past two decades. 3.4–7.2 % of children and adolescents are thought to have ADHD in general [96]. ADHD is characterized by symptoms of excitability, lack of attention, and excessive impulsivity. The causes of ADHD are multifaceted, involving a range of factors such as genetic, environmental and perinatal complications [97]. Additionally, ADHD frequently accompanying with autism spectrum disorder (ASD), with 20–50 % of children with ADHD also meeting criteria for ASD, and 30–80 % of those with ASD meeting criteria for ADHD [98]. ADHD is frequently treated with medicine that targets specific dopamine, noradrenaline, and serotonin neurotransmission systems [99]. Psychostimulants like methylphenidate (MPH), are the primary treatment cure moderate to severe instances of ADHD in children and young adults. However, common challenges include side effects, social resistance to medication, negative perception of ADHD, and poor adherence to medications [100,101]. In a 12-week randomized double-blind placebo-controlled clinical trial, *Bifidobacterium bifidum* (*Bf-688*) has resulted in enhanced neuropsychological performance in children with ADHD. Children with ADHD were divided into two groups; one receiving add-on *Bf-688* (daily bacterial count of 5×10^9 CFUs) ($n = 51$) and the other receiving a placebo

($n = 51$). The group receiving the *B. bifidum* supplementation shown significant improvements in mental parameters. Gut microbiome analysis revealed a significant increase in the *Firmicutes* to *Bacteroidetes* ratio (*F/B* ratio) only in the *Bf-688* group. There were also reductions in the biosynthesis of N-Glycan [102]. In another triple-blind, randomized controlled trial of 60 Iranian ADHD patients aged four to sixteen. The participants were randomly assigned to receive probiotics supplements containing both *Lactobacillus plantarum PTCC 1896*™ (A7) and *Bifidobacterium animalis* subsp. *Lactis* (BB-12®) (n = 30) or placebo (n = 30) for 8 weeks. ADHD symptoms were assessed using *Conners' Parent Rating Scale (CPRS)* and *Integrated Visual and Auditory Continuous Performance Test (IVA/CPT)* at baseline and during the study. There was a significant decrease in the CPRS total score after 4 weeks in the probiotic group (baseline: 43.96 ± 21.52; fourth week: 37.22 ± 23.01; p = 0.01). However, no significant changes were observed in the CPRS total score after 8 weeks. Additionally, auditory response was also improved in the probiotic group as compared to the placebo group [103].

4.4. Alzheimer disorder

Alzheimer's disease (AD) is a major health issue globally which affects approximately 50,000,000 people worldwide. It is the most common reason of dementia [104]. The disease is marked by the gradual buildup of beta amyloid (Aβ) plaques and tangled clusters of hyperphosphorylated tau neurofibrils, which result in neuroinflammation and a steady decline in cognitive abilities [105]. Synaptic dysfunction and neuronal death are partly driven by excessive or unresolved immune system activation. Additionally, infections or traumatic events like traumatic brain injury can disturb central immune balance and speed up disease progression [106]. Despite various hypothesis about the causes and development of Alzheimer's disease, both its onset and progression are not fully understood. As a result, a number of therapeutic remedies have failed to generate significant benefits [107–109]. It is widely believed that early diagnosis is crucial for intervention at the initial stages of the disease; however, reliable and consistent biomarkers for early detection are still not available for clinical use [110,111]. Recently, the gut microbiota has been highly explored as the center of biomedical research and it has become a potential therapeutic intervention for various disorders affecting the central nervous system, including AD [112,113]. Supplementation of *Lactobacillus plantarum* (LBP) have been studied to alter the composition of gut microbiota, inflammatory markers, short-chain fatty acids (SCFAs), amyloid-β and enhance cognitive functioning in AD animal models [114,115]. LBP strain such as MTCC1325 also delayed degeneration of neurons and may revert all the constituents of ATPase enzymes in AD-induced rat brain [116]. Supplementation with *Lactobacillus plantarum* PS128 protects against damage caused by intracerebroventricular injection of streptozotocin by modulating the levels of propionic acid, glycogen synthase kinase 3 beta activity, and gliosis in 3 × Tg-AD mice. Thus, PS128 supplementation may be a promising approach to prevent and/or slow the progression of Alzheimer's disease [117]. In another study, *Bifidobacteria* alleviated behavior abnormalities and stabilized gut dysbiosis in AD mouse, offering a novel probiotic dietary strategy for potentially delaying Alzheimer's disease progression. Treatment with *Bifidobacterium breve* CCFM1025 and WX significantly enhanced synaptic plasticity and increased levels of brain-derived neurotrophic factor (BDNF), fibronectin type III domain-containing protein 5 (FNDC5), and post-synaptic density protein 95 (PSD-95). Additionally, the microbiome and metabolomic profiles of the mice suggests the role of gut–brain axis in the disease's pathology [118]. Similar findings were reported in a 2018 study involving 25 CE patients who were given probiotics at a dosage of 3×10^9 CFU for 12 weeks, with one capsule administered every other day. The study noted improvements in TYM scores (Test Your Memory), cognitive function, serum glutathione levels, and 8-OHdG levels in the serum of Alzheimer's patients [119].

5. Clinical trials of potential psychobiotic strains

5.1. Human studies

A number of studies have been carried out to study the effects of psychobiotics on mental health. In a double-blind, randomized, placebo-controlled study, 80 boys (aged 7–15) suffering from autism spectrum disorder (ASD) were given *Lactobacillus plantarum* PS128 for 4 weeks. There was a significant improvement in opposition/defiance behaviors in the treated group as compared to the placebo group [120]. In another study, consumption of a fermented milk product with probiotic (FMPP) having a blend of probiotics including *Lactococcus lactis* subsp. *Lactis, Streptococcus thermophilus, Lactobacillus bulgaricus* and *Bifidobacterium animalis* subsp. *lactis* had a positive impact on emotional centers in healthy female volunteers after 4 weeks [121]. In another study, a total of 156 healthy adults facing subclinical symptoms of depression, anxiety, and insomnia were randomly divided into two groups and were assigned to receive either NVP-1704 (mixture of *Lactobacillus reuteri* NK33 and *Bifidobacterium adolescentis* NK98) ($n = 78$) or a placebo ($n = 78$) for eight weeks. In NPV-1704 group, there was alleviation of depression and anxiety symptoms in comparison of placebo group. There was also significant reduction in the levels of serum interleukin-6 in NPV-1704 group. Additionally, NPV-1704 also improved sleep quality and levels of *Bifidobacteriaceae* and *Lactobacillacea* in the gut [122]. In a randomized, placebo-controlled, two-arm, parallel, double-blind design, *Bifidobacterium longum* (BL) NCC3001 (1×10^{10} CFU/daily) was given to 45 healthy adults with mild-to-moderate stress for 6 weeks. There was a reduction in the perceived stress and improvement in the subjective sleep quality score of probiotic group as compared to the placebo group [123]. Table 1 showed the human studies highlighting the potential role of psychobiotics in different mental disorders.

5.2. Animal studies

A number of clinical trials has been conducted on animals, particularly on mice. Different bacterial strains have shown amazing results against different psychological disturbances (Table 2). In a six-week study, *Bifidobacterium longum* 1714 and *Bifidobacterium breve* decreased the psychoactive disorders in innately anxious BALB/c mice [73]. In another study, *Pediococcus acidilactici* strain CCFM6432 resulted in inhibition of stress-induced anxiety-like behaviors in chronically stressed mice in five weeks. It controlled the improper expression of hippocampal phosphorylated CREB and the c-Fos protein, in addition to the mitigation of HPA axis hyperactivity. In particular, CCFM6432 inhibited the over-grown pathogenic bacteria (*e.g.*, *Escherichia-shigella*) in the gut resulting in improved microbial composition and increasing beneficial bacteria (*e.g.*, *Bifidobacterium*) [,139]. Birmann et al. [140] reported significant decrease in depression-like behavior in adult male swiss mice supplemented with *Komagataella pastoris* KM71H. The yeast worked by modulating the permeability of the blood-brain barrier, mRNA levels of the Nuclear factor kappa B, Interleukin 1β, Interferon γ, and Indoleamine 2 3- dioxygenase, and prevention of oxidative stress and plasma corticosterone levels. In another study, diabetic rats were fed a combination of probiotics (*Lactobacillus acidophilus, Bifidobacterium lactis and Lactobacillus fermentum*) for two months which resulted in reverting deteriorated brain functions in the levels of cognitive performances and their proposed synaptic mechanisms in diabetes mellitus [141]. In a chronic restraint stress depression model, adult specific pathogen free (SPF) Sprague–Dawley rats were exposed to 21 days of restraint stress followed by behavioral testing. *Lactobacillus helveticus* NS8 was supplemented throughout the experiment. There was improvement in chronic restraint stress-induced behaviors and cognitive dysfunction through modulation of microbiota-gut-brain axis [84]. From the studies conducted on maternal separation (MS) models of mice, it has been investigated that psychobiotics can clearly lessen the widespread effects of early life stress (ELS) on the developing nervous

Table 1
Review of clinical trials conducted on humans to study the pyschobiotics and their beneficial psycological effects.

S. No.	Type of study	No of participants	Duration of study	Bacteria	Dose	Findings	Mechanism	References
1	Randomised, double-blind, placebo controlled, multi-centre, pilot clinical study	40	90 days	*Bacillus coagulans* MTCC 5856	2×10^9 cfu (2 billion spores)	Strong efficacy for the patients suffering from irritable bowel syndrome and major depressive disorder	Synthesis of SCFAs and compounds with antibacterial and anti-inflammatory properties	[124]
2	Repeated measures, placebo-controlled design	22	4 weeks	*Bifidobacterium longum* 1714	1×10^9 CFU/day	Decreased stress and enhanced memory	Production of Brain-Derived Neurotrophic Factor (BDNF) through vagal activation	[125]
3	A randomized, double-blind, placebo-controlled study	44	6 weeks	*Bifidobacterium longum* NCC3001	1×10^{10} CFU/g	Decrease in depression and low response to negative emotional stimuli in different areas of brain	BDNF regulation and secretion of neuroactive compounds	[126]
4	Randomized, open-label study	40	8 weeks	*Clostridium butyricum* MIYAIRI 588	60 mg/day	Effective against treatment-resistant major depressive disorder and also reduced depression	Controlled release of proinflammatory agents	[127]
5	Randomised, double-blinded, placebo-controlled trial	20	8 weeks	*Lactobacillus casei* Shirota	1×10^9 over 8 weeks	Reduction in the perceived stress scale, cognitive state anxiety scores and somatic state	Not studied	[128]
6	A double-blind, placebo-controlled, parallel-group trial	51	8 weeks	*Lactobacillus casei* Shirota	100 mL of a fermented beverage containing more than 1×10^9 CFU/mL/day	Prevention of onset of physical symptoms and no increase in Salivary cortisol and plasma L-tryptophan levels as compared to the placebo group. Significant increase in fecal serotonin levels of treated group	Modulation of HPA axis	[129]
7	Not given	32	5 weeks	*Lactobacillus gasseri* CP2305	1×10^{10} CFU	Stress-associated behaviors and sleeping quality was enhanced. Additionally, the supplementation of probiotics inhibited increases in stress-responsive microRNA expression and basal salivary cortisol release	Regulation of inflammation mechanisms	[130]
8	Three-arm parallel design, placebo-controlled, double-blind Randomized 121 Controlled Trial (RCT)	81	8 weeks	*Bifidobacterium longum* R0175 and *Lactobacillus helveticus* R0052	1×10^9 CFU/5 g	The Beck Depression Inventory (BDI) score reduced significantly	Modulation of neurotransmitters synthesis and metabolism	[131]
9	Randomized, double blind, placebo-controlled trial (RCT)	110	8 weeks	*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175	$\geq 10 \times 10^9$ CFU/5 g	Significant reduction in depression symptoms in patients suffering from depression	Gut microbiota mediated effect on brain-derived neurotrophic factor (BDNF)	[132]
10	A randomised, double-blind, placebo-controlled study	79	12 weeks	*Lactobacillus plantarum* P-8	$2x10^{10}$ CFU/sachet/day	Alleviation of stress/anxiety	Gut microbiota mediated alteration of nuerotransmitter synthesis	[133]
11	Not given	90	3 weeks	*Lactobacillus plantarum* JYLP-326	1.5×10^{10} CFU per sachet	Reduction in anxiety, depression and insomnia	Metabolism regulation of gut microbiota	[134]
12	Randomised, double-blind, placebo-controlled study	111	12 weeks	*Lactobacillus plantarum* DR7	1×10^9 cfu/day	Decrease in symptoms of anxiety ($P = 0.001$), stress ($P = 0.024$) and total psychological scores ($P = 0.022$)	Reduction in levels of plasma cortisol and pro-inflammatory cytokines	[135]
13	Randomized, double-blind and placebo-controlled study	103	12 weeks	*Lactobacillus plantarum* P8	10 log CFU daily	Significant decrease in stress, anxiety, memory and cognitive symptoms	Remarkable reduction in pro-inflammatory cytokines such as IFN-γ and TNF-α	[136]
14	Randomized double-blind placebo-controlled intervention trial	12	21 days	*Lactobacillus rhamnosus* Probio-M9	2.5×10^{10} CFU/g	Enhanced mental and physical well-being	Enhanced diversity of the gut microbiota of the hosts	[137]
15	Double-blind, randomized, placebo-controlled study	70	8 weeks	Heat-killed *Lactobacillus paracasei* PS23	10 billion HK-PS23 cells/capsule	Improvement in perceived anxiety states	Decreased blood cortisol levels	[138]

Table 2
Review of preclinical studies conducted on rodent models to study the pyschobiotics and their beneficial psycological effects.

Sr. No.	Type of model, duration of experiment	Bacteria	Dose	Findings	Mechanism	References
1	Five-week-old C57BL/6J female mice, 21 days	*Weissella paramesenteroides* WpK4	10^8 CFU	Significant decrease in anxiety and depressive like states	Through inflammatory modulation	[144]
2	30 male C57BL/6 mice, 28 days	*Lactobacillus plantarum* WLPL04	10^9 CFU/mL of drinking water	Alleviation of anxiety/ depressive-like behaviors and cognitive dysfunctions	Increased production of 5 hydroxytrytamine (5-HT), (BDNF) and tropomyosin-related kinase B (TrkB)	[145]
3	5C7BL/6J male mice (3 week-old), 28 days	*Lactobacillus johnsonii* BS15	1×10^9 cfu	Prevention of restraint stress-induced hippocampus-related memory dysfunction	Modulation of hypothalamic–pituitary–adrenal axis (HPA-axis) by lowering the serum corticosterone level, enhanced levels of neurotransmitters and prevention of apoptosis and oxidative stress	[146]
4	5 weeks	*Bifidobacterium breve* CCFM1025	10^9 CFU mL^{-1}	Reduction in depressive-like behaviors of chronically stressed mice and control of neurological abnormalities	Increased levels of neuroactive metabolites like tryptophan, hypoxanthine, and nicotinate. CCFM1025 also has a wider carbohydrate utilization capacity	[83,139]
5	C57BL/6 male mice, 3 weeks	*Akkermansia muciniphila*	5×10^8 colony-forming unit (CFU)/ml	Decrease in depressive behavior in mice arised due to chronic restraint stress (CRS)	Modulation of hormones and neurotransmitters like BDNF. It also altered serum metabolism and composition of gut microbiota	[147]
6	Rat maternal separation (MS) model, 4 weeks	*Bifidobacterium infantis* 35624	1×10^{10} live bacterial cells/100 mL drinking/ day	Normalization of behavioral and immune responses. It also restored the concentrations of basal noradrenaline in the brain	Anti-inflammatory properties	[148]
7	Adult male F344 rats, 8 weeks	*Lactobacillus casei* Shirota	1×10^9 CFU/mL	Significant reduction in levels of salivary cortisol and physical symptoms It also resulted in decreased production of corticotrophin releasing factor in paraventricular nucleus	Regulation of HPA axis	[149]
8	BALB/c mice, 2 weeks	*Bifidobacterium adolescentis* 150 and *Lactobacillus plantarum* 90sk	1×10^7 CFU of *Bifidobacterium adolescentis,* 150 and 1×10^8 CFU of *Lactobacillus plantarum* 90sk	Lowered depressive-like behavior in the forced swimming test	GABA production	[150]
9	Sixty male Sprague-Dawley (SD) rats, 11 weeks	*Faecalibacterium prausnitzii* ATCC 27766	1×10^9 CFU by oral gavage	Prevention and treatment of stress and anxiety	Enhanced levels of cytokines (IL-10) and SCFAs in the plasma and cecum. In addition, normalized levels of interleukin-6, C- reaction protein, corticosterone	[151]
10	Male Sprague-Dawley rats, 4 weeks	*Lactobacillus helveticus* NS8	1×10^9 CFU/mL in drinking water	Reduction of stress in hyperammonia-treated rats with decreased levels of serotonin in hippocampal regions	Down regulation of serotonin metabolism and inflammation	[152]
11	Male Wistar rats, 8 weeks	*Lactobacillus plantarum* ATCC 8014	1×10^7 CFU/mL	Enhanced production of brain-derived neurotrophic factor (BDNF) serotonin in amygdala. Positive effects were reported in the elevated plus maze and forced swimming tests	Modulation of HPA axis to reduce oxidative stress	[153]
12	Male BALB/c mice	*Lactobacillus rhamnosus* JB-1	l 1 $\times 10^9$ CFU	Alleviation of restricted behaviors associated with anxiety and depression with reduction in levels of corticosterone	Regulation of the HPA axis and GABA production	[57]
13	BALB/cJ house mice, 2 weeks	*Lactobacillus rhamnosus* GG	1×10^9 CFU	Attenuation of obsessive compulsive like behavior in treated mice	Modulation of serotogenic system of brain	[154]

system. Psychobiotic combination of *Lacticaseibacillus (L.) rhamnosus* Rosell®-11 and *Lactobacillus (L.) helveticus* Rosell®-52 (Lacidofil®) has shown psychoactive properties in rats suffering from maternal separation. When Sprague-Dawley rat pups received Lacidofil® treatment for 3 h a day from post-natal day (PND) 4–19, there was a significant reduction in negative consequences of the disease [142]. *Limosilactobacillus fermentum* CECT 5716 controlled the levels of corticosterone produced from maternal stress which resulted in improvement of exploratory behavior in the EPM test. This strain also helped in restoring the intestinal barrier by decreasing the permeability of small intestine and preserving tight-junction integrity in rats [143]. In a study, 48 healthy rats were given *Lactobacillus plantarum* MTCC1325 (12×10^8 CFU/mL; 10 mL/kg body weight) for 60 days. There was a significant reduction in level of acetylcholine in addition to morphometric and behavioral changes which highlights the anti-alzheimer properties of *Lactobacillus plantarum* MTCC1325 [114].

6. Commercial status of psychobiotics

According to study conducted by Future Market Insights, the

psychobiotic supplements market is likely to achieve at a compound annual growth rate (CAGR) of 3.70 % by the year 2033. Based on Forecasts, the market will increase from US$ 140.3 million in 2023 to US $ 201.8 million in 2033. The regions covered for the forecast include Middle east, North America, Western Europe, Africa, Eastern Europe, Japan, Asian pacific and South America. Probiotic supplements have already achieved a great place in the market worldwide. The global demand for probiotics is growing significantly due to the increasing popularity among people about their direct impacts on digestive health and highly nutritious in nature. The market has also seen a significant hike in interest in the unique probiotic subclass known as psychobiotics, as several commercial products have been introduced by various companies across the globe. Despite being studied extensively at the laboratory levels for various psychoactive abilities, the market share of the commercial psychobiotics is still lagging. There are various factors affecting the commercialization of psychobiotics. Several companies are marketing different formulations which are discussed in Table 3.

7. Future perspectives

Although these multi-probiotics molecule has been shown to be effective in various pre-clinical and clinical trials, the results are not totally reliable. For instance, these substances don't work well on volunteers suffering from down spirited mood [155]. The most of the research on psychobiotics has been carried out on its efficacy, and there is insufficient data to support its safety. According to Sotoudegan's study of probiotics in the human body, probiotics may lead to several negative effects, such as gastrointestinal dysbiosis, systemic infection, the creation of toxic metabolisms, etc [156]. So, its risk–benefit assessment is a major step prior to its use on patients. Second, although there are few studies which assessed the efficiency and safety of psychobiotics, the assessment principles were different. Probiotics confer low side effects

Table 3
List of different commercially available psychobiotics in market.

Sr. No.	Name of formulation	Manufacturing company	Organisms	Amount of bacteria	Effect
1	SBO Probiotics Mental Clarity	Ancient Nutrition	*Bacillus coagulans* SNZ-1969, *Saccharomyces boulardii* SNZ-1986, *Bacillus subtilis* SNZ-1972, *Bacillus clausii* SNZ-1971	25 billion CFU/ capsule	Delivers healthy stress support; Supports cognitive function; Improves digestive and immune system
2	Brainbiotic	Natural Stacks	*Lactobacillus helveticus* R0052, *Lactobacillus plantarum, Lactobacillus brevis, Bifidobacterium longum* R0175	6 billion CFU/ capsule	Claim to deal with stress and foggy brain. It also enhances memory and digestion
3	Mood Probiotic	Innovixlabs	*Lactobacillus helveticus* Rosell 52ND, *Bifidobacterium longum* Rosell −175	15 billion CFU/ capsule	It may aids in reducing psychological and physical symptoms of stress
4	Mood & Stress Probiotic	Floradapt	*Lactobacillus plantarum* DR7	1 billion CFU	Favours the gut-brain axis promoting a healthy mood; Supports stress reduction
5	SBO MOOD BOOST	Lifted NATURALS	*Bacillus coagulans, Bacillus indicus & Bacillus subtilis*	3 billion CFU	Formulated to support mood health, digestive health, and immune health
6	Mood Lift Probiotic + Prebiotic	NOURISH LABS	*Bacillus coagulans*	2 billion CFU	Improve digestive system, elevate energy, mood and brain functions, increase gut bacteria
7	Mood Boosting Probiotic	Blood Balance	*Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus plantarum, Lactobacillus paracasei, Saccharomyces boulardii*	40 billion CFU	Supports digestive and immune health. It also enhances mood and gut health
8	Mood plus	Garden of life Dr. Formulated Probiotics	*Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175 with 14 probiotic strains	50 billion CFU/ capsule	Helps in stress management and attaining emotional stability
9	Psychobiotic PS128®	Bened Biomedicals and OptiBiotix	*Lactobacillus plantarum* subsp. *plantarum* PS128®	30 billion CFU/ capsule	It can prevent mental and movement disorders including anxiety, autism, depression, Parkinson's disease, insomnia and irritable bowel syndrome etc
10	Psychobiotics	VacuuBiome TM	*Lactobacillus rhamnosus, Bifdobacterium longum, Lactobacillus plantarum, Lactobacillus reuteri, Lactobacillus casei, Bifidobacterium breve*	50 billion CFU/g	It supports emotional well-being, mood relaxation, and stress reduction. It also helps in restoring brain dysfunctioning
11	Mood Super Strains free for sensitive patients	LIFTED Naturals	*Lactobacillus rhamnosus* GG, *Bifidobacterium longum*	30 billion CFU/ capsule	Prescribed for depression and anxiety
12	Daily uplifter	Uplift Food	*Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175 Organic prebiotic blend	4 billion CFU/ capsule	It promotes cheerful mood and brain health through gut health
13	ZenBiotic	Entheozen	*Bifidobacterium animalis* subsp. *lactis* (BS01), *Bacillus subtilis* DE111, *Lactobacillus plantarum* (Lp-115), *Lactobacillus brevis* (Lbr-35), *Bacillus coagulans* (LactoSpore), *Lactobacillus rhamnosus* (Lr-32), *Bifidobacterium longum* (BI-05), *Lactobacillus helveticus, Lactobacillus casei* (Lc-11), *Lactobacillus acidophilus* (La-14) and *Bifidobacterium breve* (Bb-03)	5 billion CFU/ capsule	It controls anxiety and depression
14	CalmBiotic	Natural Factors	*Lactobacillus helveticus* R0052 *Bifdobacterium longum* R0175	3 billion CFU/ capsule	Helps to control occasional nervousness and stress. It also promotes healthy mood balance
15	Mood Probiotic	Amen	*Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus helveticus, Lactobacillus paracasei, Lactobacillus casei, Lactobacillus brevis, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus gasseri, L Lactobacillus salivarius, Bifidobacterium lactis, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis*	51 billion CFU/ capsule	It supports gut-brain axis. It also promotes calm behavior

and it might take more time for evaluation. It does not provide immediate results like conventional medicines which cause uncertainty about its positive impact in the brief time period. For the peoples suffering from major disorders, medicines are the foremost preference, and probiotics are a better options as follow-up prescriptions after controlling the illness. Thus, using probiotics as an adjuvant appears to be a novel method of treating mental illnesses. Hence there are some issues which needs proper research and justification in order to provide a significant place in medicine in future. First, the majority of studies are conducted on animal models and there is a need switch from animal studies to human studies for better results. Second, the trials are conducted on small scale which are inconsistent in providing convincing results. Extensive clinical research is needed to propose the dose, treatment period, efficiency and strain preference for treatment of depressive disorders using probiotics. Furthermore, the clinical outcomes of probiotics have primarily been assessed based on the phenotype and the answers to questionnaires; without confirming the biological indicators. Additional diagnostic techniques for mood disorders in people are necessary. Finally, the use of multiomics tools to collect and compare data between healthy and unhealthy peoples will be more helpful to elucidate genetic, molecular, and target pathway for potential interventions.

8. Conclusion

The novel class of probiotics 'Psychobiotics' has the potential to control anxiety/stress and mood swings. A number of bacteria has been studied to communicate through gut-brain axis regulation under various psychological conditions. They employ a variety of mechanism like modulation of hypothalamic-pituitary-adrenal (HPA) axis, by directly influencing immune system and through production of various neurotransmitters and neurohormones. Psychobiotics also holds good share in market by number of commercially available products by different companies. Despite being a lot of research, there are still many questions which need to be answered. There is further need of studies related to humans in order to accept psychobiotics over the conventional medicines.

CRediT authorship contribution statement

Neel Kamal: Writing – original draft, Methodology, Formal analysis, Data curation. **Baljeet Singh Saharan:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Formal analysis, Conceptualization. **Joginder Singh Duhan:** Visualization, Validation, Supervision, Investigation, Formal analysis. **Ashwani Kumar:** Writing – review & editing. **Payal Chaudhary:** Formal analysis, Data curation. **Chhaya Goyal:** Formal analysis, Data curation. **Mukesh Kumar:** Software, Methodology. **Nikita Goyat:** Formal analysis. **Meena Sindhu:** Investigation, Formal analysis. **Priti Mudgil:** Writing – review & editing, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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