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Review Article

Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders

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ABSTRACT

Psychobiotics are a group of probiotics that affect the central nervous system (CNS) related functions and behaviors mediated by the gut-brain-axis (GBA) via immune, humoral, neural, and metabolic pathways to improve not only the gastrointestinal (GI) function but also the antidepressant and anxiolytic capacity. As a novel class of probiotics, the application of psychobiotics has led researchers to focus on a new area in neuroscience. In the past five years, some psychobiotics strains were reported to inhibit inflammation and decreased cortisol levels, resulting in an amelioration of the symptoms of anxiety and depression. Psychobiotics are efficacious in improving neurodegenerative and neurodevelopmental disorders, including autism spectrum disorder (ASD), Parkinson's disease (PD) and Alzheimer's disease (AD). Use of psychobiotics can improve GI function, ASD symptoms, motor functions of patients with PD and cognition in patients with AD. However, the evidence for the effects of psychobiotics on mental and neurological conditions/disorders remains limited. Further studies of psychobiotics are needed in order to determine into their effectiveness and mechanism as treatments for various psychiatric disorders in the future.

1. Introduction

The human gut contains 10^{14} microorganisms, a value that is 100 times greater than the number of cells in the human body [1,2]. Gut microbiota have been reported to be involved in various physiological processes, including immunomodulation, energy balance and activation of the enteric nervous system (ENS) [3–7]. The individual's profile of microbiota is controlled by factors including diet, genetics, sex, and age

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[5,8]. The microbiota plays critical roles in human health. In particular, dysbiosis of the gut microbiota is correlated to various diseases of the central nervous system (CNS). For instance, lower *Bifidobacterium* and/or *Lactobacillus* counts were observed in subjects with major depressive disorder [9–11]. In addition, a decreased number of *Bifidobacterium* was observed in the gut microbiota of patients with Alzheimer's disease (AD) [12]. According to a recent study, the relative abundances of anti-inflammatory bacteria, including the genera *Blautia*, *Roseburia* and *Coprococcus*, were significantly lower in fecal samples from patients with Parkinson's disease (PD) [13]. Children with autism spectrum disorder (ASD) have been found with lower relative abundances of microbiota and lower overall bacterial diversity [14]. Furthermore, dysregulation of gut microbiota increases the risk of developing the attention deficit hyperactivity disorder (ADHD) [15,16].

The evidence of microbiota-gut-brain axis (MGBA) communication can be found from the relationship between gut dysbiosis with functional gastrointestinal disorders and central nervous disorders [17]. Communication between the gut and brain has been identified, and the emotional state is impacted by the function of the GI tract [18,19]. Dysregulation of the MGBA has been reported to correlate with neuropsychological, GI, and metabolic disorders [19]. According to a review article of Burokas et al., the brain and the gut microbiota may bidirectionally communicate via neurotransmitters, immunomodulation, the ENS and short chain fatty acids (SCFAs) [20]. Decreased social interactions of germ-free (GF) animals compared with specific pathogen-free (SPF) controls demonstrated the concept of MGBA [21]. Transplantation of a standard microbiota into GF mice improves social deficits further evidenced the importance of gut microbiota to CNS function [22].

2. Psychobiotics

In 2013, Dinan and colleagues defined the term "psychobiotics" as a novel class of probiotics that suggest potential applications in treating psychiatric diseases [23]. The majority of psychobiotic research is performed using animal studies which induce stress and conduct behavioral tests to rodents to evaluate motivation, anxiety, and depression [3]. Psychobiotics may regulate the neurotransmitters and proteins, including gamma-aminobutyric acid (GABA), serotonin, glutamate and brain-derived neurotrophic factor (BDNF), which play important roles in controlling the neural excitatory-inhibitory balance, mood, cognitive functions, learning and memory processes [24–26]. Sudo and colleagues described a crucial role of the microbiota and hypothalamic-pituitary-adrenal axis (HPA). Slight restraint stress of GF mice induces excess release of corticosterone and adrenocorticotropic hormone compared with the SPF mice [27]. In addition, the exaggerated proinflammatory cytokines activate the HPA axis, enhance the permeability of blood-brain barrier (BBB), and decrease the level of serotonin, which lead to psychiatric conditions such as depression [28,29]. Some strains of *Lactobacillus* spp. and *Bifidobacterium* spp., such as *Lactobacillus brevis*, *Bifidobacterium dentium* and *Lactobacillus plantarum* produce GABA and serotonin [30–32]. In addition, strains of *Lactobacillus*, such as *L. plantarum* and *Lactobacillus odontolyticus* produce acetylcholine [33]. Recently, it has been found that serotonin synthesis in the gut can be regulated by microbes. For instance, spore-forming bacteria from the gut microbiota have been found to induce serotonin biosynthesis from gut enterochromaffin cells [34]. Those probiotics are worthy of study to elucidate their psychobiotic potential, particularly in psychiatric disorders. In this review, we summarized the potential applications of psychobiotics to psychiatric disorders and suggested possible directions for future research.

3. Psychobiotics in mental health

Good mental health represents a status of mental, psychological well-being. Proposed by Dinan and colleagues, the application of psychobiotics may require a precision strategy for targeting anxiety and depression behaviors [23]. A growing body of evidence showed that psychobiotics have the psychotropic effects on depression, anxiety and stress (Table 1). Several probiotics strains were reported as psychobiotics from animal studies. The administration of *Lactobacillus plantarum* PS128 (PS128) reduced anxiety and depression-like behaviors of mice. PS128 significantly decreased inflammation and corticosterone levels. Notably, administration of PS128 significantly increased levels of dopamine and serotonin in the prefrontal cortex and striatum compared with control mice [35,36]. The administration of the single strain *Lactobacillus helveticus* NS8 reduced anxiety, depression and cognitive dysfunction. In addition, *L. helveticus* NS8 increased the serotonin, norepinephrine (NE) and brain-derived neurotrophic factor (BDNF) levels in the hippocampus [37]. Using single strain of *B. longum* 1714 decreased the stress, depression and anxiety behaviors [38]. The *Lactobacillus rhamnosus* (JB-1) could decrease anxiety and depression. In particular, the intake of JB-1 leads to region-dependent alterations in GABA receptor expression in the brain and reduces the plasma corticosterone (CORT) level [39]. The administration of the single strain *Bifidobacterium longum* NCC3001 is effective on treating anxiety. In addition, the expression of BDNF in the hippocampus is upregulated after the administration of the single strain *B. longum* NCC3001 [40]. Using a signal strain of *Bacterium infantis* 35624 is effective on depression-like behaviors [41].

In addition to promising animal studies, several research has found positive effects of probiotics on mental health in humans. Healthy volunteers who were administered *Bifidobacterium longum* 1714 for 4 weeks exhibit reduced stress and improved memory [42]. A randomized, double-blind, placebo-controlled trial investigated the effects of probiotic yogurt (*Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12) and probiotic capsules (*Lactobacillus casei*, *L. acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum* and *Streptococcus thermophiles*) on petrochemical workers [43]. Recipients using both probiotic yogurt and probiotic capsules exhibited improved mental health parameters by assessing the depression anxiety and stress scale (DASS) general health questionnaire (GHQ). A probiotic combination of *L. helveticus* R0052 plus *B. longum* R0175 reduces anxiety and depression in healthy subjects compared with the control [44]. In addition, the urinary free

Table 1 – Psychobiotics reported for mental health.

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
ELS mice N = 10/group	*L. plantarum* PS128 10^9 CFU/mouse/day by gavage	16 days	• SPT • OFT • EPM • FST • Monoamines and metabolites • Serum specimens	Locomotor activity ↑ Anxiety-like behaviors in naïve mice ↓ Depression-like behaviors in ELS mice ↓ Corticosterone levels in ELS mice ↓ TNF-α and IL-6 ↓ IL-10 ↑ Dopamine and serotonin levels in the prefrontal cortex ↑	[35]
Germ-free mice N = 10/group	Heat-killed or live *L. plantarum* PS128 10^9 CFU/mouse/day by gavage	16 days	• OFT • EPM • FST • Monoamines and metabolites • Serum specimens	Live: Locomotor activity ↑ Anxiety-like behavior ↓ Dopamine and serotonin levels in the striatum ↑ Heat-killed: NA	[36]
Male SPF CRS rats N = 8/group	*L. helveticus* NS8 10^9 CFU/ml in drinking water	21 days	• SPT • EPM • OFT • ORT • OPT • Brain monoamine neurotransmitters • Plasma	Anxiety and depression ↓ Cognitive dysfunction ↓ Plasma CORT and ACTH levels ↓ Plasma IL-10 levels ↑ Serotonin and NE levels and BDNF expression in the hippocampus ↑	[37]
Male BALB/c mice N = 22/group	*B. longum* 1714 or *B. breve* 1205 10^9 CFU/day by gavage	21–41 days	• SIH • DMB • EPM • OPT • TST • FST	*B. longum* 1714: Stress ↓ Depression ↓ Anxiety ↓ *B. breve* 1205: Anxiety ↓	[38]
Male BALB/c mice N = 16/group	*L. rhamnosus* (JB-1) 10^9 CFU/mouse/day by gavage	28 days	• OFT • SIH • EPM • FST	Depression ↓ Anxiety ↓ Plasma CORT levels ↓ GABA receptor ($GABA_{b1b}$) expression in cortical regions ↑ and in the hippocampus, amygdala and locus coeruleus ↓ ($GABA_{A\alpha 2}$) expression in the prefrontal cortex and amygdala ↓ Hippocampus ↑ The effect of probiotics was abolished by vagotomy	[39]

Male T-muris-infected AKR mice *L. rhamnosus:* N = 10 *B. longum:* N = 16 Placebo: N = 16	*L. rhamnosus* NCC4007 or *B. longum* NCC3001	10 days	• light/dark preference test • Step-down test	*Bifidobacterium longum* NCC3001: Anxiety-like behavior ↓ BDNF expression in the hippocampus ↑ Circulating cytokine levels: NA	[40]
MS rats Control: N = 7 Probiotics: N = 8	*B. infantis* 35624 1×10^{10} CFU/100 ml in drinking water	45 days	• FST • Plasma samples	Depression ↓ CORT: NA Tryptophan and tryptophan metabolites: NA	[41]
Healthy male volunteers (Mean age: 25.5) N = 22	*B. longum* 1714 1×10^{9} CFU/day	4 weeks	• Cohen Perceived Stress Scale • PAL test • EEG • SECPT	Stress ↓ Hippocampus-dependent visuospatial memory performance ↑ Frontal midline electroencephalographic mobility ↑	[42]
Petrochemical workers (Age: 20–60 years) N = 70 Probiotic yogurt + placebo capsule: Men = 12 Women = 13 Conventional yogurt + probiotic capsule: Men = 12 Women = 13 Conventional yogurt + placebo capsule: Men = 12 Women = 8	Probiotic yogurt: *L. acidophilus* LA5 and *B. lactis* BB12 1×10^{7} CFU/day Conventional yogurt: *S. thermophilus* and *L. bulgaricus* Probiotic capsule: 1. *L. casei* 3×10^{3}, 2. *L. acidophilus* 3×10^{7}, 3. *L. rhamnosus* 7×10^{9}, 4. *L. bulgaricus* 5×10^{8}, 5. *B. breve* 2×10^{10}, 6. *B. longum* 1×10^{9}, 7. *S. thermophiles* 3×10^{8} CFU/day/capsule	6 weeks	• Randomized, double-blind, placebo-controlled study • GHQ-28 • DASS	In both the probiotic yogurt + placebo capsule and conventional yogurt + probiotic capsule groups: DASS ↓ GHQ ↓ ACTH: NA	[43]
Male Wistar rats N = 12/group Healthy subjects (Age: 30–60 years) N = 55 Probiotics: Men = 7 Women = 19 Placebo: Men = 7 Women = 22	*L. helveticus* R0052 and *B. longum* R0175 Rats: 10^{9} CFU/rat/day by gavage Humans: 3×10^{9} CFU/stick/day	Rats: 14 days Humans: 30 days	Rats: • Conditioned defensive burying test Humans: • Double-blind, controlled, randomized, parallel study • HSCL-90 • HADS • PSS • CCL • 24 h UFC	Rats: Anxiety-like behavior ↓ Humans: Somatization ↓ Anxiety and depression ↓ Anger-hostility ↓ Problem solving ↑ Median urinary free cortisol level ↓	[44]

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Table 1 – (continued)

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Healthy subjects (UFC levels are less than baseline values) N = 25	*L. helveticus* R0052 and *B. longum* R0175 3×10^9 CFU/stick/day	30 days	• HSCL-90 • HADS • PSS • CCL • 24 h UFC	Anxiety and depression ↓	[45]

ELS: Early life stress; SPT: Sucrose preference test; OFT: Open field test; EPM: Elevated plus maze; FST: Forced swimming test; NA: not applicable; PAL: Paired Associate Learning; EEG: Electroencephalography; SECPT: Socially evaluated cold presser test; GHQ: General health questionnaire; DASS: Depression anxiety and stress scale; ATCH: Adrenocorticotropic hormone; SPF: specific-pathogen-free; CRS: chronic restraint stress; ORT: Object recognition test; OPT: Object placement test; CORT: corticosterone; NE: norepinephrine; BDNF: brain-derived neurotrophic factor; SIH: Stress-induced hyperthermia; DMB: Defensive marble burying; TST: Tail suspension test; HCL-90: Hopkins Symptom Checklist; HADS: Hospital Anxiety and Depression Scale; PSS: Perceived Stress Scale; CCL: Coping Checklist; UFC: urinary free cortisol; MS: Maternal separation.

cortisol level is significantly decreased by the *L. helveticus* R0052 plus *B. longum* R0175 intervention [45].

Some ongoing clinical studies are investigating the effects of probiotic supplements (*L. plantarum* PS128, *L. plantarum* 299v, *L. rhamnosus* GG, Bifihappy, Vivomixx®, Probio'Stick, etc.) on depression and anxiety [46–52]. These studies will evaluate the state of inflammation, stress and mood of recipients.

Possible communication pathways between brain and gut microbiota were immunoregulatory, neuroendocrine, and vagus pathways [53]. Probiotics intervention such as *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* can decrease the levels of inflammatory cytokines [54]. The anti-immunoregulatory effects of probiotics have been reported to activate the population of T regulatory cell as well as the secretion of IL-10 [23]. In addition, probiotics contact with gut epithelium enteroendocrine cells (EECs) to produce neuropeptides and neurotransmitter such as peptide YY (PYY), neuropeptide Y (NPY), substance P, serotonin, glucagon-like peptide-1 and -2 (GLP-1 and GLP-2), and cholecystokinin [55,56]. Approximately 95% of serotonin is derived from gut enterochromaffin cells and ENS neurons, which is associated with the regulation of GI secretion and motility [57]. In addition, the brain serotonin pathways are involved in regulating cognition and mood [58]. Therefore, dysfunctional serotonin pathways may contribute to the comorbidity of GI and mood disorders. Although the aforementioned studies have shown some promising evidence regarding the potential prospects of psychobiotics, the data from humans remains limited. Further clinical studies are needed in this area.

4. Psychobiotics in neurodegenerative disorders

4.1. *Alzheimer's disease (AD)*

AD is a chronic neurodegenerative disorder characterized by cognitive and memory impairments [59]. The evidence on the effects of probiotics on ameliorating cognitive disorders are limited. In Table 2, we summarize the effects of psychobiotics on AD. In a recent work Agahi et al. investigated the effect of probiotic administration on patients with severe AD [60]. The results found that severe AD patients were insensitive to probiotic supplementation. One explorative intervention study using multiple strains, *L. casei* W56, *Lactococcus lactis* W19, *L. acidophilus* W22, *B. lactis* W52, *L. paracasei* W20, *L. plantarum* W62, *B. lactis* W51, *B. bifidum* W23 and *L. salivarius* W24 on subjects with AD [61]. The gut bacteria composition and tryptophan metabolism in serum were influenced by probiotics intervention. Recently, Bonfili and colleagues found that administration of probiotic formulation (SLAB51) on transgenic AD mice significantly reduced the oxidative stress by inducing SIRT-1-dependent mechanisms [62]. Two studies investigated the effect of multiple strains, *L. acidophilus, Lactobacillus fermentum, B. lactis* and *B. longum*, on an animal model of AD. The total counts of *Bifidobacterium* spp. and *Lactobacillus* spp. were increased and *Coliform* was decreased in the stool after the probiotic intervention. Furthermore, probiotic supplementation improves learning and memory deficits in AD rats compared with control rats. Reductions in

Table 2 – Psychobiotics reported for Alzheimer's disease.

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Subjects with severe AD (Age: 65–90 years) Control group Male = 10 Female = 13 Probiotic group Male = 17 Female = 18	Capsule one: *L. fermentum*, *L. plantarum* and *B. lactis* Capsule two: *L. acidophilus*, *B. bifidum*, and *B. longum* Total dosage of 3×10^9 CFU/day	12 weeks	• Randomized, double-blind, and placebo-controlled clinical trial • TYM • Biochemical parameters	Serum NO, GSH, TAC, MDA and 8-OHdG: NA Cytokines (TNF-α, IL-6, and IL-10): NA	[60]
Subjects with AD (Mean age: 76.7 years) Male = 11 Female = 9	Probiotic supplements: *L. casei* W56, *Lactococcus lactis* W19, *L. acidophilus* W22, *B. lactis* W52, *L. paracasei* W20, *L. plantarum* W62, *B. lactis* W51, *B. bifidum* W23 and *L. salivarius* W24.	4 weeks	• Open-labeled • MMSE • CDT • Serum and feces specimens	Fecal zonulin ↓ *Faecalibacterium* and *prausnitzii* ↑ Serum kynurenine ↑ Serum tryptophan, phenylalanine and tyrosine: NA	[61]
Male transgenic AD mice (3xTg-AD) N = 64	SLAB51: *S. thermophilus*, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, *L. brevis* 200bn bacteria/Kg/day in drinking water	16 weeks	• Sirtuin-1 activity • RARβ acetylation • Redox enzyme activity • Oxyblot analysis	Brain tissue: SIRT1 activity and expression ↑ Level of acetylated p53 and total p53 ↓ Level of acetylated RARβ and total RARβ ↓ Activity of antioxidant enzymes (GST, GPx, SOD and CAT) ↓ Protein and lipid oxidation ↓ The level of Cleaved PARP, OGG1, 8-OHdG ↓	[62]
Male Wistar rats receiving intrahippocampal injections of Amyloid beta (Aβ1-42) N = 12 per group	*L. acidophilus* (1688FL431-16LA02), *L. fermentum (ME3)*, *B. lactis* (1195SL609-16BS01) and *B. longum* (1152SL593-16BL03) 10^{10} CFU/day in drinking water	8 weeks	• MWM • Bacterial count in stool samples • Amyloid plaque detection • SOD, CAT activities and MDA level detection	Stool samples: Total *Coliform* count ↓ Total *Bifidobacterium* count ↑ Total *Lactobacillus* count ↑ Learning and memory ↑ Amyloid plaques ↓ Inflammation and oxidative stress ↓ MDA and SOD levels ↓ Catalase levels: NA	[63]
Male Wistar rats receiving intrahippocampal injections of Amyloid beta (Aβ1-42) N = 12 per group	*L. acidophilus*, *L. fermentum*, *B. lactis* and *B. longum* 10^{10} CFU/day in drinking water	8 weeks	• HOMA-IR • The serum lipid profile biomarkers	Insulin level ↓ Insulin resistance ↓ Serum TG level: NA	[64]
Male ICR mice N = 5 per group	Fermented cow's milk containing *L. fermentum* (LAB9, LAB10) (CM-LAB9) or *L. casei* (LABPC) 10^9 CFU/0.2 ml by oral gavage	28 days	• MWM • Biochemical analyses • Cytokine measurement	Learning and memory behaviors ↑ Antioxidant levels (SOD, GSH, and GPx) ↑ MDA, AChE and pro-inflammatory cytokine levels ↓	[65]
Wistar rats with D-galactose-induced AD N = 6 per group	*L. plantarum* MTCC1325 12×10^8 CFU/ml; 10 ml/kg body weight	60 days	• MWM • Gross Behavioral Activity • Biochemical Estimation of Cholinergic System	Cognitive Behavior ↑ Gross Behavioral Activity ↑ The cortex and hippocampus: ACh ↑ AChE ↓	[66]

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Table 2 – (continued)

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Subjects with AD (Age: 60–95 years) N = 30 per group Male = 6 Female = 24	Probiotic milk: 1. *L. acidophilus* 2. *L. casei* 3. *B. bifidum* 4. *L. fermentum* 2×10^9 CFU/day	12 weeks	• Randomized, double-blind, and controlled clinical trial (IRCT20151130562 3N60) • NINDS-ADRDA • MMSE • HOMA-IR • HOMA-B • QUICKI • Biochemical parameters	Improvement in cognition (MMSE) Plasma MDA level ↓ hs-CRP level ↓ Changes in insulin resistance, β-cell function and insulin sensitivity	[67]

TYM: Test Your Memory; MWM: Morris water maze; MDA: Malondialdehyde; NO: nitric oxide; GSH: glutathione; TAC: total antioxidant capacity; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; CDT: Clock drawing test; MMSE: Mini-mental state examination; SIRT1: Sirtuin-1; GPx: Glutathione peroxidase; GST: Glutathione S-transferase; CAT: Catalase; SOD: Superoxide dismutase; NA: not applicable; RARβ: Retinoic acid receptor-β; PARP: poly (ADP-ribose) polymerase-1; OGG1: 8-Oxoguanine glycosylase; HOMA-IR: Homeostasis model assessment of insulin resistance; TG: triglycerides; Ach: Acetylcholine; AChE: Acetylcholinesterase; HOMA-B: Homeostatic model assessment for β-cell function; QUICKI: Quantitative insulin sensitivity check index; hs-CRP: High-sensitivity C-reactive protein in serum.

the number of amyloid plaques, inflammation and oxidative stress were observed in the Alzheimer-probiotics group [63]. The administration of probiotics decreases the insulin level and insulin resistance compared to the control. However, no significant difference in serum triglyceride (TG) levels is observed between control- and probiotic-treated AD rats [64]. In addition, a treatment with cow's milk fermented with *L. fermentum* (LAB9, LAB10) (CM-LAB9) or with *L. casei* (LABPC) increases learning, memory behavior and antioxidant levels (SOD, GSH, and GPx). The levels of pro-inflammatory cytokines, malondialdehyde (MDA) and AChE are reduced in the probiotic group compared to the control group [65]. A single strain of *L. plantarum* MTCC1325 not only improves cognitive behaviors and gross behavioral activities but also restores the level of acetylcholine (ACh) in D-galactose-induced AD rats [66]. One randomized, double-blind, and controlled clinical trial found that consumption of probiotic-treated milk (*L. acidophilus, L. casei, B. bifidum* and *L. fermentum*) decreased the plasma MDA and serum high-sensitivity C-reactive protein (hs-CRP) levels. The insulin resistance, beta-cell function and insulin sensitivity were changed by the probiotic intervention in recipients with AD. Notably, the Mini-Mental State Examination (MMSE) score was significantly improved after administration of the probiotic treatment [67].

Based on the findings from animal studies, probiotics use ameliorates cognitive and memory deficits compared with the control [63,65,66]. The systemic inflammation was reduced after probiotics intervention. One possible mechanism may be mediated through SIRT1 pathway [62]. In addition, a probiotic supplement has been shown to improve the cognition of recipients with AD [67]. These studies show some evidence of probiotics treatment on AD. However, one study showed inconsistent effects of probiotic supplement on severe AD patients [60]. Further studies are need that into consideration of factors such as severity of AD and age in order to gain a better understanding of the efficacy of probiotics to treat AD.

4.2. *Parkinson's disease (PD)*

PD is a neuropsychiatric disorder that influences approximately two percent of the elderly population [68]. Constipation is a common nonmotor symptom of patients with PD [69–71]. In Table 3, we summarize the effects of psychobiotics on PD. In a randomized, double-blind, placebo-controlled clinical trial, subjects with PD were administered a probiotic supplement containing *L. acidophilus, B. bifidum, Lactobacillus reuteri,* and *L. fermentum* for 12 weeks. The probiotic consumption group exhibited a decreased score on the Unified Parkinson's Disease Rating Scale (UPDRS) compared to the placebo group. In addition, the consumption of probiotics not only significantly reduced the hs-CRP and MDA levels but also increased the glutathione (GSH) levels. Notably, probiotic consumption significantly improved the insulin function compared with the placebo [72]. One randomized controlled study focused on inflammation, insulin and lipid-related genes in peripheral blood mononuclear cells (PBMCs) from subjects with PD. After a 12-week intervention, subjects with PD who received the probiotic supplement displayed a significant downregulated expression of interleukin-1 (IL-1), IL-8 and tumor necrosis factor alpha (TNF-α) and upregulated

Table 3 – Psychobiotics reported for Parkinson's disease.

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Subjects with PD (Age: 50–90 years) N = 60 Probiotics: N = 30 Placebo: N = 30	*L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* each 2×10^9 CFU Total 8×10^9 CFU/day	12 weeks	• Randomized, double-blind, placebo-controlled clinical trial (IRCT2017082434497N4) • Movement Disorders Society-Unified • MDS-UPDRS • hs-CRP • HOMA-IR • QUICKI • Blood samples	MDS-UPDRS ↓ hs-CRP levels ↓ MDA levels ↓ GSH levels ↑ Insulin levels ↓ Insulin resistance ↓ Insulin sensitivity ↑ Triglyceride, VLDL and HDL levels: NA	[72]
Subjects with PD Probiotics: N = 25 Placebo: N = 25	Probiotic supplements: 8×10^9 CFU/day	12 weeks	• Randomized, double-blind, placebo-controlled clinical trial • PBMC	IL-1, IL-8 and TNF-α levels ↓ TGF-β and PPAR-γ levels ↑ LDLR and VEGF levels: NA	[73]
Subjects with PD and Rome III–confirmed constipation N = 120	Fermented milk: Prebiotic fiber and multiple probiotic strains: 1. *S. salivarius* subsp *thermophilus* 2. *Enterococcus faecium* 3. *L. rhamnosus* GG 4. *L. acidophilus* 5. *L. plantarum* 6. *L. paracasei* 7. *L. delbrueckii* subsp *bulgaricus* 8. *B. breve* 9. *B. animalis* subsp *lactis* 250×10^9 CFU/day	4 weeks	• Randomized, double-blind, placebo-controlled trial (NCT02459717) • UPDRS Part III	CBMs ↑ Constipation ↓	[74]
Subjects with PD (Mean age: 76.05 years) Male = 17 Female = 23	*L. acidophilus* and *B. infantis* tablet/twice/day	3 months	• Hoehn and Yahr scale • NMS-Quest	Abdominal pain ↓ Bloating ↓	[75]
Subjects with PD N = 40	Milk fermented with *L. casei* Shirota 6.5×10^9 CFU/day	5 weeks	• Two randomized controlled trials • Rome III criteria	Improvement of stool consistency and bowel habits Abdominal pain and bloating ↓ Sensation of incomplete emptying ↓	[76]

MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; hs-CRP: High-sensitivity C-reactive protein; HOMA-IR: Homeostasis model of assessment-estimated insulin resistance; QUICKI: Quantitative insulin sensitivity check index; MDA: Malondialdehyde; GSH: Glutathione; NA: not applicable; PBMC: Peripheral blood mononuclear cells; IL-1: Interleukin-1; TNF-α: tumor necrosis factor alpha; TGF-β: Transforming growth factor beta; PPAR-γ: peroxisome proliferator-activated receptor gamma; LDLR: Low-density lipoprotein receptor; VEGF: vascular endothelial growth factor; CBMs: Complete bowel movements; NMS-Quest: Non-motor symptoms questionnaire.

expression of transforming growth factor beta (TGF-β) and peroxisome proliferator-activated receptor gamma (PPAR-γ) compared with the placebo control. However, no effect was found on probiotic intake to the expression of vascular endothelial growth factor (VEGF), low-density lipoprotein receptor (LDLR) or the markers of inflammation and oxidative stress [73]. Three studies found that recipients with PD who were using probiotics exhibited improved gastrointestinal functions. Subjects with PD who ingested fermented milk containing multiple strains of probiotics exhibited an amelioration of constipation [74]. Treatment with a probiotic combination of *L. acidophilus* and *B. infantis* significantly reduced abdominal pain and bloating [75]. Additionally, patients with PD exhibited improved stool consistency and bowel habits after 5 weeks of treatment with fermented milk containing *L. casei* Shirota [76].

An ongoing open-label pilot study is investigating the effect of PS128 on patients with PD (Hoehn and Yahr stage: 1–2.5). The primary outcome will be measured with the UPDRS (Part III) motor score after the administration of 60 billion colony-forming units (CFU) of the PS128 intervention for 12 weeks. In addition, the secondary outcome will be measured with the Nonmotor Symptoms (NMS-Quest) score and the Patient Global Impression of Change (PGIC) score [77]. Another randomized, double-blind, placebo-controlled clinical trial is recruiting patients with PD to evaluate improvements in constipation induced by probiotic capsule containing *B. lactis*. The primary outcome will be assessed on amelioration of the frequency of stool movements every week after the administration of the probiotic intervention for 4 weeks. The secondary outcome will be assessed on improvements in the constipation severity score (ROME IV criteria), patient's quality of life (PAC-QOL questionnaire) and stool consistency (Bristol stool chart) [78].

The majority of clinical studies of probiotics in patients with PD have been focused on gastrointestinal function [74–76,78]. Only one study reported that probiotics improved the movement of patients with PD [72]. It has been found that oxidative stress and inflammations were increased in the severity of PD [79]. The aforementioned studies have showed promising effects of psychobiotics by reducing oxidative stress and the inflammations in patients with PD. One of the critical pathological features of PD are Lewy bodies formation of dopaminergic neurons which cause by accumulation of misfolded α-synuclein protein [80]. Recently, Chandra and colleagues reported that α-synuclein was expressed in the enteroendocrine cells [81,82]. It is possible that misfolded α-synuclein first produces in enteroendocrine cells and propagates to the nervous system. Evaluation of the effect of probiotic supplements on abnormal α-synuclein in enteroendocrine cells are suggested in future investigations on PD.

5. Psychobiotics in neurodevelopmental disorders

5.1. *Autism spectrum disorder (ASD)*

ASD, a neurodevelopmental disorder, is characterized by deficits in social communication and social interactions across multiple contexts, accompanied by restricted and repetitive patterns of behaviors, interests, and/or activities [83].

The global prevalence of ASD has been estimated to be one in 160 children. Patients with ASD frequently experience gastrointestinal (GI) symptoms, diarrhea and constipation [84]. It has been shown that probiotics could improve the GI symptoms and even the ASD-related symptoms in patients with ASD. By searching the top 5 primary registries accepted by the International Committee of Medical Journal Editors (ICMJE) in the WHO network, 10 clinical trials using probiotics interventions have been registered to date (Table 4).

The effects of some multiple strain probiotic products on patients with ASD have been investigated. Visbiome extra strength is a probiotic product which contains 8 strains of probiotics, including *L. acidophilus* DSM24735™, *L. plantarum* DSM24730™, *Lactobacillus paracasei* DSM24733™, *L. helveticus* DSM24734™, *Streptococcus thermophilus* DSM24731™, *B. lactis* DSM24736™, *B. breve* DSM24732™, and *B. lactis* DSM24737™. In 2016–2017, the effects of Visbiome on GI symptoms in children with ASD were investigated [85]. Another product containing multiple probiotic strains, Vivomixx, is being used in 2 ongoing trials in patients with ASD. The primary outcome of the trial conducted in Italy is the change in the severity of ASD measured using ADOS-2 [86]. Subjects will be divided into 2 groups: those with GI symptoms and those without GI symptoms. Subjects will take 2 packets/day of the intervention for 1 month and 1 packet for additional 5 months. The other trial conducted in UK is a crossover trial [87]. Subjects will be assigned to either a probiotic or placebo group for 4 weeks, followed by 4 weeks of washout. After washout, the subjects will crossover to the other group for 4 weeks. This study uses ATEC to measure the changes in ASD symptoms. Vivomixx contains 450 billion lyophilized bacterial cells belonged to 8 probiotic strains, *S. thermophiles* DSM 24731, *B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737, *L. acidophilus* DSM 24735, *L. plantarum* DSM 24730, *L. paracasei* DSM 24733, and *Lactobacillus delbrueckii* subsp. *bulgaricus* DSM 24734, per sachet. Vivomixx and Visbiome contain the same 8 strains of probiotics, according to the deposition number of the probiotics. An open-label trial conducted in Egypt used 3 probiotics strains, *L. acidophilus*, *L. rhamnosus*, and *B. longum*, and assessed their effects on GI and ASD symptoms [88]. According to recently published results of the study, the severity of autism and GI symptoms, as assessed using ATEC and 6-GSI, respectively, were improved after the 3-month intervention with probiotics [88]. The effects of a probiotic product containing *B. lactis* BB-12 (BB-12) and *L. rhamnosus* GG (LGG) (BB-12 + LGG) on ASD was also investigated. A placebo-controlled trial conducted in the US investigating the adverse events of BB-12 + LGG as the primary outcome in children with ASD is in progress [89]. Adverse events will be assessed using a case report form. Another placebo-controlled trial aimed to survey the safety of 2 doses of the probiotic formulation (10^{10} and 10^{11} CFU). This study comprised a 56-day intervention with probiotics or placebo and a subsequent 28-day observational stage without the intervention. This study is yet to recruit patients [90]. A probiotic product (Gastrus) containing 2 *L. reuteri* strains (DSM 17938 and ATCC PTA 6475) will be investigated for its effects on ASD symptoms in Japan

Table 4 – Clinical trials investigating probiotic interventions in patients with ASD[a].

Intervention and duration	Registry and status	Primary outcomes	Secondary outcomes	Subjects number and age	Study location
1. Probiotics (Visbiome extra strength) 2. Placebo (maltose) Duration: Intervention for 8 weeks, followed by 3 weeks washout and crossover for 8 weeks	ClinicalTrials.gov (NCT02903030) [85] Completed	Gastrointestinal (GI) Module of the PedsQL	• Target Symptom Rating • Parent Anxiety Checklist-ASD • ABC • SRS • CSHQ • PSI Short Form	3–12 years Probiotics group: 6 Placebo group: 6	United States
1. Probiotics (Vivomixx) 2. Placebo (maltose) Duration: 2 packets for 1 months followed by 1 packet for 5 months	ClinicalTrials.gov (NCT02708901) [86] Recruiting	ADOS-2	• GI symptomatology • Electroencephalogram (EEG; power, coherence, and asymmetry) • Serum levels of lipopolysaccharide, leptin, resistin, TNF-α, IL-6, and Plasminogen Activator Inhibitor-1 (PAI-1) • Fecal calprotectin level • Global ASD symptomatology: repetitive behaviors and sensory profiles (CARS and SCQ) • Developmental Quotient • Adaptive Functioning (VABS) • Behavioral profiles (CBCL 1.5–5) • Parental Stress (PSI)	18–72 months Expected numbers of subjects: 1. Subjects with GI symptoms GI-Probiotics group: 25 GI-Placebo group: 25 2. Subjects without GI symptoms NGI-Probiotics group: 25 NGI-Placebo group: 25	Italy
1. Probiotics (Vivomixx, 4.5×10^{12} CFU) 2. Placebo (maltose; dietary supplement) Duration: Intervention for 4 weeks, washout for 4 weeks and crossover for 4 weeks	ClinicalTrials.gov (NCT03369431) [87] Recruiting	ATEC	• GIH • ABC • APSI	3–16 years Expected numbers of subjects: Probiotics group: 41 Placebo group: 41	United Kingdom
1. Probiotics (BB-12 + LGG, 10^9 CFU of each) 2. Placebo (maltodextrin) Duration: 84 days	ClinicalTrials.gov (NCT02674984) [89] Recruiting	Adverse events assessed using a case report form	• ABC and SRS-2 for irritability and maladaptive behaviors	4–15 years Expected numbers of subjects: Probiotics group: 20 Placebo group: 10	United States
1. High dose of BB-12 + LGG (10^{11} CFU) 2. Low dose of BB-12 + LGG (10^{10} CFU) 3. Placebo (maltodextrin) Duration: Intervention for 56 days and observation for 28 days	ClinicalTrials.gov (NCT03514784) [90] Not yet recruiting	Adverse events (safety survey from a case report form)	• Irritability and maladaptive behaviors (ABC and SRS-2)	4–15 years Expected numbers of subjects: High dose group: 28 Low dose group: 28 Placebo: 14	United States
Probiotics (*L. acidophilus*, *L. rhamnosus* and *B. longum*), 10^8 CFU/gram Duration: 5 g/day for 3 months	Japan registries network (JPRN) (UMIN000026157) Completed Result published [88]	1. 6-GSI 2. ATEC	–	5–9 years Open-label, 30 subjects (19 boys and 11 girls)	Egypt

(*continued on next page*)

Table 4 – (*continued*)

Intervention and duration	Registry and status	Primary outcomes	Secondary outcomes	Subjects number and age	Study location
1. Probiotics (*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475; Gastrus), 4×10^8 CFU, twice a day 2. Placebo Duration: 6 months	Japan registries network (JPRN) (UMIN000033113) [91] Not yet recruiting	1. VABS 2. ABC	• QPGS-RIII • Oxytocin level in urine • Diversity of the microbiome	6–18 years Expected number of subjects: 100	Japan
1. Probiotics (*L. plantarum* WCFS1), 4.5×10^{10} CFU/g 2. Placebo Duration: once daily for 6 weeks	ISRCTN (ISRCTN04516575) [92] Completed	1. Gut microbiota 2. Diversity and dynamics of lactic acid bacteria and clostridia	• GI symptoms • Behavior	4–16 years The protocol did not provide the number of subjects.	United Kingdom
1. Probiotics (*L. plantarum* PS128), 3×10^{10} CFU/capsule 2. Placebo (microcrystalline cellulose), twice daily Duration: 28 days	Australia and New Zealand (ACTRN12616001002471) [94] Completed	1. ABCT 2. SRS 3. CBCL	• CGI-I • SNAP-IV • Gut microbiota • Urine metabolomics analysis	7–15 years Subjects are boys with ASD. Probiotics group: 40 Placebo group: 40	Taiwan
Intervention: 1. Oxytocin (drug) 2. Probiotics (*L. reuteri*) 3. Placebo (Vitamin C) Duration: Probiotics and placebo for 24 weeks, the last 12 weeks will add oxytocin spray to each group	ClinicalTrials.gov (NCT03337035) [95] Not yet recruiting	1. Social communication and behavior (ADOS, ADI-R, SRS, ATEC) 2. Social behavior (ABC)	• Oxytocin level in blood • Structural and functional MRI • Autonomic indices (blood volume pulse, heart rate variation, peripheral skin temperature, and skin electrodermal activity)	5–15 years Expected numbers of subjects: Probiotics group: 30 Placebo group: 30	United States

[a] Study status updated on October 30, 2018.

ABC: Aberrant Behavior Checklist; ABC-T: Autism Behavior Checklist-Taiwan Version; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; APSI: Autism Parenting Stress Index; ATEC: Autism Treatment Evaluation Checklist; CBCL: Child Behavior Checklist; CARS: Childhood Autism Rating Scale; CHI-I: Clinical Global Impressions-Improvement; CSHQ: Children's Sleep Habits Questionnaire; GIH: Gastrointestinal History; MRI: Magnetic Resonance Imaging; PedsQL: Pediatric Quality of Life Inventory; QPGS-RIII: Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS) based on Rome III Criteria; SCQ: Social Communication Questionnaire; SRS: Social Responsiveness Scale.

(UMIN000033113 [91]). The primary outcomes of this study are VABS and ABC for the ASD clinical psychiatric evaluation.

The use of single probiotic strain in an ASD study was also recorded. *L. plantarum* WCFS1 was used in a placebo-controlled trial conducted in the UK in 2012 [92]. This study recruited patients with ASD presenting with GI problems for a 6-week intervention with either probiotics or placebo. The dose of the probiotics is not provided and the study results are not available. However, Parracho et al. reported the results of *L. plantarum* WCFS1 in a double-blind, placebo-controlled, crossover study that investigated effects of *L. plantarum* WCFS1 on children with ASD in 2010 [93]. This study was conducted in the United Kingdom without registration and the primary outcome of this study was not presented. According to the report, 17 subjects completed the trial and *L. plantarum* WCFS1 improved behavior- and communication-related problems, as assessed using the Development Behaviour Checklist (DBC). It was shown that the administration of the *L. plantarum* WCFS1 intervention for 3 weeks altered the gut microbiota. In 2016, *L. plantarum* PS128 (PS128) was used in a double-blind, placebo-controlled trial conducted in Taiwan investigating the effects of PS128 on boys with ASD (ACTRN12616001002471 [94]). Eighty subjects were included and randomly assigned to either the PS128 (3×10^{10} CFU/capsule, 2 capsules/day) group or the placebo (microcrystalline as placebo capsule, 2 capsules/day) group for the 28-day intervention. A source of bias in this study is that only boys with ASD were included. Results of the study are not yet available. The effects of a single probiotic strain in combination with an oxytocin spray will be investigated in children with ASD in the US [95]. Subjects will receive either probiotics, *L. reuteri*, or the placebo, vitamin C, for two phases of the first 12-week intervention. In the second phase, all subjects will receive an oxytocin spray accompanied by the original probiotic/placebo intervention for further 12 weeks. Primary outcomes of this trial are social communication and behavior assessments. The level of oxytocin in blood will be analyzed as the secondary outcome.

According to the registered information, different species and strains of probiotics have been used in individual trials (Table 4). Either multiple strains or single strains of probiotics were reported to exhibit beneficial effects on children with ASD [88,93]. Safety assessment was the primary outcome for the administration of BB-12 + LGG to children with ASD in more than one trial. Probiotic products with the same formulation but different names (Vivomixx and Visbiome) may be expected to produce similar results in ASD trials. Currently, limited data are available that reveal the effects of probiotics on patients with ASD.

5.2. *Attention deficit hyperactivity disorder (ADHD)*

ADHD is a brain disorder of which the most common symptoms are inattention, hyperactivity and impulsivity. In Table 5, we summarized the effects of psychobiotics on ADHD. According to Pärtty and colleagues, infants who received *L. rhamnosus* GG exhibited a reduced risk of developing ADHD [96]. As shown in one case study, Truehope GreenBAC improves the mood and energy levels of patients with ADHD [97]. In addition, food supplement treatments containing *L.*

Table 5 – Psychobiotics reported for ADHD.

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Infants N = 75	*L. rhamnosus* GG (ATCC 53103) 1×10^{10} CFU/day	6 months	• Randomized, double-blind, placebo-controlled prospective follow-up study (NCT00167700) • Gut microbiota • ICD-10	Incidence of ADHD later in childhood ↓ *B.* species bacteria in feces ↓	[96]
A 24-year-old female with ADHD	Truehope GreenBAC: 1. *L. rhamnosus* A 2. *L. delbrueckii* sub. *ulgaricus*b 3. *L. rhamnosus* B 4. *B. longum* 5. *L. acidophilus* 6. *B. breve* 7. *L. casei* 8. *S. thermophiles* Two capsule/day	2 months	• MADRS • CAARS	Improved mood and energy levels *Candida* infection ↓	[97]
Children with AD/HD N = 10 group	*L. acidophilus*	4 weeks	• IVA/CPT • FSRCQ • FSACQ • DSM-IV • CPRS-R:L	Prudence, consistency, and stamina ↑ Vigilance, focus, and speed ↑ Auditory Response, Visual Response, Auditory Attention and Visual Attention ↑	[98]

ICD-10: International Classification of Diseases; MADRS: Montgomery-Asberg Depression Rating Scale; CAARS: Conners' Adult ADHD Rating Scale; IVA/CPT: Intermediate Visual and Auditory/Continuous Performance Test; FSRCQ: Full Scale Response Control Quotient; FSACR: Full Scale Attention Control Quotient; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; CPRS-R:L: Conner's Parent Rating Scale - Revised: Long Form.

Table 6 – Psychobiotics reported for insomnia.

Study model	Psychobiotics, dosage and route of administration	Duration of probiotics administration	Test	Observation summary	Reference
Healthy Japanese male subjects (Age 41–69 years) N = 17	Heat-killed *L. brevis* SBC8803 (SBL88™) capsule/day	10 days	• Non-randomized, double blind, placebo-controlled, and crossover pilot study • AIS • EEG • BDI	AIS and EEG: NA Sleep journal scores: Waking, turning over, and tooth grinding ↓ Delta power value in 40s subjects ↑	[110]
C3H-HeN mice N = 6 per group	Heat-killed *L. brevis* SBC8803	4 weeks	• EEG • EMG	Nighttime wheel-running activity and duration of wakefulness ↑ NREM sleep during the active phase ↓ The duration of NREM sleep during the resting phase ↑	[109]
Healthy elderly subjects (Age: 60–81 years) N = 29	Fermented milk with *L. helveticus* CM4	3 + 3 weeks	• Prospective, randomized, double-blind and placebo-controlled, with a crossover design • SF-36 health survey	Improvement of sleep efficiency and number of wakening episodes SF-36 scores: NA	[111]

NA: not applicable; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; AIS: Athens Insomnia Scale; EEG: Electroencephalograms; EMG: Electromyographic; NREM: Non-rapid eye movement; SF-36: Short Form 36.

acidophilus improve the self-control and attention of children with ADHD [98].

An ongoing double-blind, placebo-controlled study is being conducted to investigate the effect of probiotic supplements on students with ADHD. The primary outcome will be assessed on symptoms of attention deficit (MOXO test) after 6 months of probiotic intake [99].

5.3. *Tourette syndrome (TS)*

TS is a neurological disorder that are typically first observed in childhood [100]. The clinical treatments of TS include behavioral treatments, α2-adrenergic agonists, antipsychotics, and deep brain stimulation (DBS) [101,102]. According to one recent case report, a fecal microbiota transplantation (FMT) dramatically ameliorates TS 8 weeks after the treatment [103].

Another randomized, double-blind, placebo-controlled clinical trial is recruiting patients to elucidate the effect of PS128 on TS [104]. The primary outcome will be measured using the Yale Global Tic Severity Scale (YGTSS) after 2 months of intervention.

6. Others

6.1. *Insomnia*

Sleep deficit has been found to induce depression, memory impairment and allergy [105–107]. Only a few reports found that using fermented products showed sleep improvements [108]. In Table 6, we summarized the effects of psychobiotics on insomnia. Two studies evaluated the effect of heat-killed *L. brevis* SBC8803 (SBL88™) on improving sleep in mice and humans. Miyazaki and colleagues reported decreased non-rapid eye movement (NREM) sleep during the active phase and enhanced NREM sleep during the resting phase following the administration of probiotics. Moreover, heat-killed *L. brevis* SBC8803 increased the duration of wakefulness and nighttime wheel-running activity [109]. As shown in the study by Nakakita et al., healthy male subjects consuming heat-killed *L. brevis* SBC8803 reported improved "walking" sleep journal scores. Furthermore, delta power values were increased in subjects aged 40 years compared with the placebo control. However, no significant effect was found on heat-killed *L. brevis* SBC8803 administration to quality of sleep (the electroencephalograms (EEG) and the Athens Insomnia Scale (AIS)) [110]. One study focused on the effect of fermented milk containing *L. helveticus* CM4 on sleep in healthy elderly subjects [111]. The intake of fermented milk significantly improved sleep efficiency and wakening episodes. No significant changes in health status and well-being of subjects (short form 36 (SF-36) health survey scores) were observed after the probiotic intervention.

7. Conclusion

An increasing number of reports have emerged and provided evidence for the effects of psychobiotics on psychiatric disorders. Some of single or multiple strains can improve CNS

functions, including mood, anxiety, depression, and the stress response, which are mediated by modulating inflammation, the HPA and neurotransmitters. Furthermore, the psychobiotic treatments have shown promising effects on neurodegenerative and neurodevelopmental disorders by altering the fecal microbiota, inflammation, oxidative state and insulin function. Probiotics may play a crucial role to regulate the aggregation of α-synuclein in enteroendocrine cells, production of microbial metabolites and activation of the vagus nerve in neurodegenerative and neurodevelopmental disorders. Thus, psychobiotic treatments could be a promising strategy to improve the quality of life for people who suffer from neurodegenerative and neurodevelopmental disorders. Further studies in this area are needed to determine the effectiveness and mechanisms of psychobiotics in order for the psychobiotics to be considered as an alternative therapy for neurodegenerative and neurodevelopmental disorders.

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