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From Probiotics to Psychobiotics: A Focused Review

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Abstract

Our microbiome consists of trillions of microorganisms. Probiotics are known to be favorable microorganisms (bacteria and yeast) to keep the gut healthy and other health effects. They have been shown to possess positive effects not only in digestion, but also on heart, brain, etc. Lately, many studies pointed out to promoting activities of probiotics in mental diseases through gut microbiota, which is so-called "psychobiome". It is now clear that bacterial inhabitants of the intestines may impact neurons and the brain through some mechanisms. Consequently, psychobiotics have been described as a new class of probiotics. In the current mini review, the role of psychobiotics is scrutinized focusing on some neurological and mental diseases.

1. Introduction

Probiotics are described as "living microorganisms that positively affect the health of the host when taken enough" by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) (Douglas & Sanders, 2008). Psychiatric disorders are associated with changes in the gastrointestinal microbiome due to effects on the central nervous system (CNS) (Jiang et al., 2015; Kelly et al., 2016). The microbiome is a multifaceted microbial ecosystem in the gut containing approximately 100 trillion microorganisms and the gut microbiome is a complicated and active ecosystem that forms mutual interactions with the host (Mangiola et al., 2016). Intestinal microbiota of individuals is affected by genetic inclination, age, type of birth, exercising habits, stress, infection, environmental features, diseases exposed, and use of antibiotics. The microbiome in gut undertakes ultimate and imperative tasks towards human health by generating a reciprocal connection amid the brain and the gut. Sturdy amount of data verifies presence of a bond between the

microbiota with metabolic diseases including diabetes, obesity as well as neurological and psychiatric illnesses such as anxiety, depression, Alzheimer's disease (AD), schizophrenia, autism, etc. The research has revealed that probiotics located in the gastrointestinal system (GI) may modulate the immune system as well as CNS. They can also generate CNS-related substances i.e. γ-aminobutyric acid (GABA), serotonin, and glutamate, which are related to the intestinal brain axis. Preclinical experiments display that some probiotic bacteria have anxiolytic and antidepressant effects (Evrensel & Ceylan, 2015). Relevantly, a psychobiotic is described as "a living organism that, when taken in sufficient quantity, provides health benefits to patients suffering from a psychiatric illness" (Tang et al., 2014). Thus, the present review aims to scrutinize psychobiotics as probiotics with psychobiotic effects that have recently become popular in scientific literature.

2. Microbiota-Intestine-Brain Axis

SCFAs (short chain fatty acids), such as propionate, acetate, and butyrate, fermented and hydrolyzed by gut microbiota, prebiotics, and dietary polysaccharides. The effect of SCFA in the microbiota on monoamines and different hormones *e.g.* serotonin (5-HT), dopamine (DA), GABA, and noradrenaline (NA) is of common interest to intestinal and brain health (Cani et al., 2013). Studies have exposed that psychobiotics can modulate neurotransmitters and proteins such as GABA, 5-HT, glutamate, and brain-derived neurotrophic factor (BDNF), which can adjust neuronal balance, sensational state, cognitive abilities, and learning (Heldt et al., 2007; Lu et al., 2008). Thus, in recent years, various psychiatric disorders (anxiety, depression, schizophrenia, mood disorder, etc.) occur, when gut-brain axis is negatively affected as consequence of the deterioration of microbiota (Erbay-Gönenir & Seçkin, 2016). Gut-brain communication takes place *via* the vagus nerve, which establishes a straight link among the brain, stomach, and intestines. Nervous, hormonal, and microbial changes in the intestines are transferred to the brain through this nerve (Wang et al., 2002).

3. Psychobiotics

In 2013, Dinan et al. outlined the term "psychobiotics" as a "*new class of probiotics*" proposed as possible solutions in the treatment of psychiatric illnesses (Dinan et al., 2013). Hence, probiotics have been found to deserve to clarify their psychobiotic properties, especially in psychiatric diseases. Most of the psychobiotic research has been performed by assessing motivation, anxiety, and depression as a consequence of the causes of stress and behavioral tests on rodents (Sarkar et al., 2016).

Psychiatric disorders may be associated with monoamine levels such as 5-HT, DA, NA, and cytokine levels in plasma in the brain (Tamam & Zeren, 2002). Thus, further research has been managed on the psychobiotic potential of these probiotics, particularly in psychiatric disorders (Cheng et al., 2019). Probiotics were first used in 1910 for the treatment of these types of ailments (Philips, 1910). Some *Bifidobacterium* spp. and *Lactobacillus* spp. strains (*i.e. L. brevis*, *L. plantarum*, and *B. dentium*) synthesize GABA from monosodium glutamate. Norepinephrine is formed by *Escherichia*, *Bacillus*, and *Saccharomyces* species, while *Streptococcus*, *Escherichia*, *Enterococcus*, and *Candida* species can synthesize 5-HT, while *Serratia* and *Bacillus* species yield DA. Recent studies

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indicated that 5-HT synthesis can be synchronized by probiotics in the gut (Schousboe & Waagepetersen, 2007; Barrett et al., 2012; O'Mahony et al., 2015). For example, spore-forming bacteria in microbiome was found to trigger biosynthesis of 5-HT released by intestinal enterochromaffin cells (Yano et al., 2015). Lower amounts of *Bifidobacterium* and/or *Lactobacillus* have been perceived in patients suffering from depression (Aizawa et al., 2016; Huang et al., 2016; Wallace & Milev, 2017). A decrease in the amount of *Bifidobacterium* was detected in the intestinal microbe flora of AD patients (Vogt et al., 2017). Another data on Parkinson's disease (PD) patients revealed that the number of bacteria with anti-inflammatory effect comprising of *Blautia*, *Roseburia*, and *Coprococcus* strains was significantly lower in their stools (Keshavarzian et al., 2015). Children with autism disorders have also been found to have a relatively lower amount of microbiota and bacterial diversity (Kang et al., 2013). In addition, dysregulation of gut microbiota was proven to upsurge the threat of developing attention deficit/hyperactivity disorder (ADHD) (Sucksdorff et al., 2015).

3.1. Psychobiotics in Mental Health

The benefit of various probiotic strains as psychobiotics to target anxiety and depression behaviors has been proven by animal studies (Dinan et al., 2013). One of them, *i.e. L. plantarum* PS128, significantly led to a decline in depression and anxiety, inflammation, and corticosterone levels, while it considerably augmented levels of DA and 5-HT in the mouse striatum and prefrontal cortex (Liu et al., 2015 & 2016). Again, *L. helveticus* NS8 reduced cognitive dysfunction, depression, and anxiety, whereas escalated 5-HT, norepinephrine, and BDNF levels in the hippocampus of Sprague-Dawley rats (Liang et al., 2015). Similarly, use of *B. longum* 1714 strain also reduced stress, depression, and anxiety behaviors (Savignac et al., 2014). Another *Lactobacillus* strain, *i.e. L. rhamnosus* (JB-1) also diminished levels of depression and anxiety and caused changes in expression of GABA receptors in the mouse brain (Bravo et al., 2011). Administration of *B. longum* NCC3001 has been found to be efficient towards anxiety and additionally upregulated BDNF level in the mouse hippocampus (Bercik et al., 2010). *Bacterium infantis* 35624 strain has been also revealed to be effective on depressive behavior in mice (Desbonnet et al., 2010).

Probiotics possessed positive effects on mental status in humans. *B. longum* 1714 was given to healthy volunteers during 4 weeks to strengthen memory and lessen stress (Allen et al., 2016). In a double-blind, randomized, and placebo-controlled clinical trial, mental health of petrochemical employees given yogurt rich in probiotics (*L. acidophilus* LA5 and *B. lactis* BB12) and capsules containing probiotics *i.e. L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. rhamnosus*, *B. longum*, *B. breve*, and *Streptococcus thermophiles*, was fortified based on data obtained from the general health questionnaire (GHQ) and the depression anxiety and stress scale (DASS). The probiotic combination prepared with *L. helveticus* R0052 and *B. longum* R0175 has been observed to diminish depression and anxiety symptoms in healthy subjects (Messaoudi et al., 2011; Mohammadi et al., 2016). Again, in other ongoing clinical trials, the outcomes of probiotics on subjects on inflammation, mood, and stress are being evaluated (Cheng et al., 2019). Possible interactions between intestinal microbiota and brain are thought to be through the

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immunoregulatory and neuroendocrine systems and vagus nerve (Li et al., 2018).

3.2. Psychobiotics in Neurological Disorders

3.2.1. Alzheimer's disease (AD)

AD is defined as a long-lasting and progressive neurodegenerative ailment portrayed by memory and cognitive deficiencies (Kumar & Singh, 2015). Gut microbiota and serum tryptophan metabolism in AD patients treated with probiotic mixture consisting of *L. acidophilus* W22, *L. lactis* W19, *L. casei* W56, *B. lactis* W52, *L. plantarum* W62, *L. paracasei* W20, *L. salivarius* W24, *B. lactis* W51, and *B. bifidum* W23 were shown to be influenced (Leblhuber et al., 2018). The probiotic formulation (SLAB51) significantly decreased oxidative stress through sirtuin-1 (SIRT-1)-related mechanisms in AD-induced transgenic mice (Bonfili et al., 2018). Probiotic supplementation led to enhancement in learning and memory in AD-induced mice (Athari Nik et al., 2018). Additionally, cow's milk fermented with *L. casei* (LABPC) or *L. fermentum* (LAB9 & 10) amended learning, memory as well as intensities of superoxide dismutase (SOD) and glutathione (GSH).

3.2.2. Parkinson's disease (PD)

PD is a neuropsychiatric disease that disturbs mainly the elderly population and manifests itself with various symptoms (De Rijk et al., 1997). In a placebo-controlled, double-blind, and randomized clinical trial, supplementation for 12 weeks with a probiotic mixture consisting of *L. reuteri, L. fermentum, L. acidophilus*, and *B. bifidum* led to a reduction in the Unified Parkinson's Disease Rating Scale (UPRDS) rating scale in the patients with PD (Tamtaji et al., 2018). In another study, improvement in bowel movements and defecation habits was observed in Parkinson's patients who consumed fermented milk inclosing *L. casei* Shirota for 5 weeks (Cassani et al., 2011). Results from another study show encouraging effects of psychobiotics by lessening oxidative damage and inflammation in PD (Shults et al., 2006).

3.2.3. Autism Spectrum Disorder (ASD)

ASD is depicted by deficiencies in public interactions in multiple situations along with limited and recurring behavioral patterns and/or actions. Accordingly, the effects of multi-strain probiotic products on ASD patients were occasionally investigated. For instance, a probiotic mixture containing *B. breve* DSM24732, *B. lactis* DSM24736, and *B. lactis* DSM24737 as well as *L. acidophilus* DSM24735, *L. helveticus* DSM24734, *L. plantarum* DSM24730, *L. paracasei* DSM24733 and *Streptococcus thermophilus* DSM24731, resulted in reduction in severity of the disease in children according to the ADOS-2 scale (Arnold, 2018). In an open-labelled clinical trial managed in Egypt, *L. acidophilus*, *L. rhamnosus*, and *B. longum* given to autistic children for 3 months caused progress in both GI symptoms and autism based on ATEC and 6-GSI scales (Shaaban et al., 2018). In another placebo-controlled and double-blind study in the UK, 3 week-administration of *L. plantarum* WCFS1 led to alterations in the intestinal microbiota by means of the Development Behavior Checklist (DBC), it was observed that it improved some problems related to behavior and communication (Parracho et al., 2010).

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3.2.4. Attention Deficit/Hyperactivity Disorder (ADHD)

The most common indications of ADHD are inattention, impulsivity, and hyperactivity (Cheng et al., 2019). According to one study, a reduced risk of developing ADHD was found in newborns given *L. rhamnosus* GG strain (Pärtty et al., 2015). Administration of dietary supplements containing *L. acidophilus* was also found to advance attention and self-control in the children diagnosed with ADHD (Harding et al., 2003).

3.2.5. Tourette Syndrome (TS)

TS is known as one of neurological diseases that typically appears firstly in childhood (Rampello et al., 2006). Clinical treatment of TS basically is carried out with α2-adrenergic agonists and antipsychotics (Weisman et al., 2013; Murphy et al., 2013). In a case report about a child diagnosed with TS, a significant improvement in TS was demonstrated after 8 weeks followed by fecal microbiota transplantation to the child (Zhao et al., 2017).

3.2.6. Insomnia

Depression, memory impairment, and even allergies can be associated with sleep deprivation (Kaneita et al., 2006; Grundgeiger et al., 2014). Miyazaki et al. (2014) reported a decrease in non-rapid eye movement (NREM) in active phase of sleep and an increase in NREM phase during the inactive phase treated with *L. brevis* SBC8803. Although positive results were obtained with the probiotic supplement *L. brevis* SBC8803 in healthy male volunteers with sleep-wandering problems, no improvement was observed in sleep quality (Nakakita et al., 2016). Another study conducted with elderly healthy people, drinking of fermented milk having the *L. helveticus* CM4 strain had a positive effect on sleep quality (Yamamuro et al., 2009).

4. Conclusion

Positive results were obtained with psychobiotic use in diseases related to the CNS, especially anxiety, depression, and stress. The data indicated that psychobiotics possess promising effects on the life quality of the patients in neurodegenerative and neurodevelopmental disorders. Information obtained *via* probing the function of psychobiotics relevant to psychiatric disorders through gut microbiota-brain axis communication is mostly based on data from animal studies. It is thought that the effects of psychobiotics on intestinal microbiota and human health will be the subject of further research in neuroscience. However, in the future, more pre-clinical and clinical research are needed to explain the mechanisms of action in the application of the concepts produced in animal models to humans and to evaluate probiotics as an alternative or complementary treatment in these disorders.

Conflicts of interest

No conflict of interest was declared by the authors.

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References

Allen, A. P., Hutch, W., Borre, Y. E., Kennedy, P. J., Temko, A., Boylan, G., ... & Clarke, G. (2016). *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Translational Psychiatry*, *6*(11), e939. doi: 10.1038/tp.2016.191.

Arnold, L. E. (2018). Probiotics for Quality of Life in Autism Spectrum Disorders. ClinicalTrials.gov Identifier: NCT02903030. https://clinicaltrials.gov/ct2/show/NCT02903030.

Athari Nik Azm, S., Djazayeri, A., Safa, M., Azami, K., Ahmadvand, B., Sabbaghziarani, F., ... & Vafa, M. (2018). *Lactobacilli* and *Bifidobacteria* ameliorate memory and learning deficits and oxidative stress in β-amyloid (1-42) injected rats. *Applied Physiology Nutrition and Metabolism*, *43*(7), 718. doi: 10.1139/apnm-2017-0648.

Barrett, E., Ross, R. P., O'Toole, P. W., Fitzgerald, G. F., & Stanton, C. (2012). γ-Aminobutyric acid production by culturable bacteria from the human intestine. *Journal of Applied Microbiology*, *113*(2), 411. doi: 10.1111/j.1365-2672.2012.05344.x.

Bercik, P., Verdu, E. F., Foster, J. A., Macri, J., Potter, M., Huang, X., ... & Lu, J. (2010). Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology*, *139*(6), 2102. doi: 10.1053/j.gastro.2010.06.063.

Bonfili, L., Cecarini, V., Cuccioloni, M., Angeletti, M., Berardi, S., Scarpona, S., ... & Eleuteri, A. M. (2018). SLAB51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. *Molecular Neurobiology*, *55*(10), 7987. doi: 10.1007/s12035-018-0973-4.

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., ... & Cryan, J. F. (2011). Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse *via* the vagus nerve. *Proceedings of the National Academy of Sciences*, *108*(38), 16050. https://doi.org/10.1073/pnas.1102999108.

Cani, P., Everard, A., & Duparc, T. (2013). Gut microbiota, enteroendocrine functions and metabolism. *Current Opinion in Pharmacology*, *13*(6), 935. doi: 10.1016/j.coph.2013.09.008.

Cassani, E., Privitera, G., Pezzoli, G., Pusani, C., Madio, C., Iorio, L., & Barichella, M. (2011). Use of probiotics for the treatment of constipation in Parkinson's disease patients. *Minerva Gastroenterologica e Dietologica*, *57*(2), 117. PMID: 21587143.

Cheng, L. H., Liu, Y. W., Wu, C. C., Wang, S., & Tsai, Y. C. (2019). Psychobiotics in mental health, neurodegenerative, and neurodevelopmental disorders. *Journal of Food and Drug Analysis*, *27*(3), 632. doi: 10.1016/j.jfda.2019.01.002.

De Rijk, M. D., Tzourio, C., Breteler, M. M., Dartigues, J. F., Amaducci, L., Lopez-Pousa, S., ... & Rocca, W. D. (1997). Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's Disease. *Journal of Neurology Neurosurgery & Psychiatry*, *62*(1), 10. doi: 10.1136/jnnp.62.1.10.

Desbonnet, L., Garrett, L., Clarke, G., Kiely, B., Cryan, J. F., & Dinan, T. G. (2010). Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. *Neuroscience*, *170*(4), 1179. doi: 10.1016/j.neuroscience.2010.08.005.

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: a novel class of psychotropic. *Biological Psychiatry*, *74*(10), 720. doi: 10.1016/j.biopsych.2013.05.001.

Erbay-Gönenir, L., & Seçkin, Y. (2016). Yeme bozuklukları. *Güncel Gastroenteroloji*, *20*(4), 473.

Evrensel, A., & Ceylan, M. E. (2015). Bağırsak beyin ekseni: psikiyatrik bozukluklarda bağırsak mikrobiyotasının rolü. *Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry*, *7*(4), 461. doi: 10.5455/cap.20150128123852.

Grundgeiger, T., Bayen, U. J., & Horn, S. S. (2014). Effects of sleep deprivation on prospective memory. *Memory*, *22*(6), 679. doi: 10.1080/09658211.2013.812220.

Harding, K. L., Judah, R. D., & Gant, C. E. (2003). Outcome-based comparison of Ritalin® *versus* food-supplement treated children with AD/HD. *Alternative Medicine Review*, *8*(3), 319. PMID: 12946241.

Heldt, S. A., Stanek, L., Chhatwal, J. P., & Ressler, K. J. (2007). Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Molecular Psychiatry*, *12*(7), 656. doi: 10.1038/sj.mp.4001957.

Huang, R., Wang, K., & Hu, J. (2016). Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*, *8*(8), 483. doi: 10.3390/nu8080483.

Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., … & Ruan, B. (2015). Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behavior and Immunity*, *48*, 186. doi: 10.1016/j.bbi.2015.03.016.

Kaneita, Y., Ohida, T., Uchiyama, M., Takemura, S., Kawahara, K., Yokoyama, E., ... & Fujita, T. (2006). The relationship between depression and sleep disturbances: a Japanese nationwide general population survey. *The Journal of Clinical Psychiatry*, *67*(2), 196. doi: 10.4088/jcp.v67n0204.

Kang, D. W., Park, J. G., Ilhan, Z. E., Wallstrom, G., LaBaer, J., Adams, J. B., & Krajmalnik-Brown, R. (2013). Reduced incidence of *Prevotella* and other fermenters in intestinal microflora of autistic children. *PloS one*, *8*(7), e68322. doi: 10.1371/journal.pone.0068322.

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Kelly, J. R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., … & Dinan, T. G. (2016). Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. *Journal of Psychiatry Research*, *82*, 109. doi: 10.1016/j.jpsychires.2016.07.019.

Keshavarzian, A., Green, S. J., Engen, P. A., Voigt, R. M., Naqib, A., Forsyth, C. B., ... & Shannon, K. M. (2015). Colonic bacterial composition in Parkinson's disease. *Movement Disorders*, *30*(10), 1351. doi: 10.1002/mds.26307.

Kumar, A., & Singh, A. (2015). A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacological Reports*, *67*(2), 195-203. doi: 10.1016/j.pharep.2014.09.004.

Leblhuber, F., Steiner, K., Schuetz, B., Fuchs, D., & Gostner, J. M. (2018). Probiotic supplementation in patients with Alzheimer's dementia - an explorative intervention study. *Current Alzheimer Research*, *15*(12), 1106. doi: 10.2174/1389200219666180813144834.

Li, Y., Hao, Y., Fan, F., & Zhang, B. (2018). The role of microbiome in insomnia, circadian disturbance and depression. *Frontiers in Psychiatry*, *9*, 669. doi: 10.3389/fpsyt.2018.00669.

Liang, S., Wang, T., Hu, X., Luo, J., Li, W., Wu, X., ... & Jin, F. (2015). Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. *Neuroscience*, *310*, 561. doi: 10.1016/j.neuroscience.2015.09.033.

Liu, Y. W., Liu, W. H., Wu, C. C., Juan, Y. C., Wu, Y. C., Tsai, H. P., ... & Tsai, Y. C. (2016). Psychotropic effects of *Lactobacillus plantarum* PS128 in early life-stressed and naïve adult mice. *Brain Research*, *1631*, 1. doi: 10.1016/j.brainres.2015.11.018.

Liu, W. H., Yang, C. H., Lin, C. T., Li, S. W., Cheng, W. S., Jiang, Y. P., ... & Tsai, Y. C. (2015). Genome architecture of *Lactobacillus plantarum* PS128, a probiotic strain with potential immunomodulatory activity. *Gut Pathogens*, *7*(1), 1. doi: 10.1186/s13099-015-0068-y.

Lu, Y., Christian, K., & Lu, B. (2008). BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of Learning and Memory*, *89*(3), 312. doi: 10.1016/j.nlm.2007.08.018.

Mangiola, F., Ianiro, G, Franceschi, F., Fagiuoli, S., Gasbarrini, G., & Gasbarrini, A. (2016). Gut microbiota in autism and mood disorders. *World Journal of Gastroenterology*, *22*(1), 361. doi: 10.3748/wjg.v22.i1.361.

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., ... & Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *British Journal of Nutrition*, *105*(5), 755. doi: 10.1017/S0007114510004319.

Miyazaki, K., Itoh, N., Yamamoto, S., Higo-Yamamoto, S., Nakakita, Y., Kaneda, H., ... & Oishi, K. (2014). Dietary heat-killed *Lactobacillus brevis* SBC8803 promotes voluntary wheel-running and affects sleep rhythms in mice. *Life sciences*, *111*(1-2), 47. doi: 10.1016/j.lfs.2014.07.009.

Mohammadi, A. A., Jazayeri, S., Khosravi-Darani, K., Solati, Z., Mohammadpour, N., Asemi, Z., ... & Eghtesadi, S. (2016). The effects of probiotics on mental health and hypothalamic-pituitary-adrenal axis: a randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutritional Neuroscience*, *19*(9), 387. doi: 10.1179/1476830515Y.0000000023.

Murphy, T. K., Lewin, A. B., Storch, E. A., & Stock, S. (2013). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(12), 1341. doi: 10.1016/j.jaac.2013.09.015.

Nakakita, Y., Tsuchimoto, N., Takata, Y., & Nakamura, T. (2016). Effect of dietary heat-killed *Lactobacillus brevis* SBC8803 (SBL88™) on sleep: a non-randomized, double blind, placebo-controlled, and crossover pilot study. *Beneficial Microbes*, *7*(4), 501. doi: 10.3920/BM2015.0118.

O'Mahony, L., Mccarthy, J., Kelly, P., Hurley, G., Luo, F., Chen, K., … & Quigley, E. M. M. (2005). *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*, *128*(3), 541. doi: 10.1053/j.gastro.2004.11.050.

Parracho, H. M., Gibson, G. R., Knott, F., Bosscher, D., Kleerebezem, M., & McCartney, A. L. (2010). A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. *International Journal of Probiotics & Prebiotics*, *5*(2), 69. (doi not available)

Pärtty, A., Kalliomäki, M., Wacklin, P., Salminen, S., & Isolauri, E. (2015). A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. *Pediatric Research*, *77*(6), 823. doi: 10.1038/pr.2015.51.

Philips, J. G. P. (1910). The treatment of melancholia by the lactic acid bacillus. *Journal of Mental Science*, *56*(234), 422. (doi not available)

Rampello, L., Alvano, A., Battaglia, G., Bruno, V., Raffaele, R., & Nicoletti, F. (2006). Tic disorders: from pathophysiology to treatment. *Journal of Neurology*, *253*(1), 1. doi: 10.1007/s00415-005-0008-8.

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, C. F., Burnet, P. W. J. (2016). Psychobiotics and the manipulation of bacteria-gut-brain signals. *Trends in Neurosciences*, *39*(11), 763. doi: 10.1016/j.tins.2016.09.002.

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Savignac, H. M., Kiely, B., Dinan, T. G., & Cryan, J. F. (2014). *Bifidobacteria* exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Neurogastroenterology & Motility*, *26*(11), 1615. doi: 10.1111/nmo.12427.

Schousboe, A., & Waagepetersen, H. S. (2007). GABA: homeostatic and pharmacological aspects. *Progress in Brain Research*, *160*, 9. doi: 10.1016/S0079-6123(06)60002-2.

Shaaban, S. Y., El Gendy, Y. G., Mehanna, N. S., El-Senousy, W. M., El-Feki, H. S., Saad, K., & El-Asheer, O. M. (2018). The role of probiotics in children with autism spectrum disorder: a prospective, open-label study. *Nutritional Neuroscience*, *21*(9), 676. doi: 10.1080/1028415X.2017.1347746.

Shults, C. W. (2006). Lewy bodies. *Proceedings of the National Academy of Sciences*, *103*(6), 1661. doi: 10.1073/pnas.0509567103.

Sucksdorff, M., Lehtonen, L., Chudal, R., Suominen, A., Joelsson, P., Gissler, M., & Sourander, A. (2015). Preterm birth and poor fetal growth as risk factors of attention-deficit/hyperactivity disorder. *Pediatrics*, *136*(3), e599. doi: 10.1542/peds.2015-1043.

Tamam, L., & Zeren, T. (2002). Depresyonda serotonerjik düzenekler. *Klinik Pskiyatri Dergisi*, *5*(4), 11. (doi not available)

Tamtaji, O. R., Taghizadeh, M., Kakhaki, R. D., Kouchaki, E., Bahmani, F., Borzabadi, S., ... & Asemi, Z. (2019). Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clinical Nutrition*, *38*(3), 1031. doi: 10.1016/j.clnu.2018.05.018.

Tang, F., Reddy, B., & Saier, M. (2014). Psychobiotics and their involvement in mental health. *Journal of Molecular Microbiology and Biotechnology*, *24*, 211. doi: 10.1159/000366281.

Vogt, N. M., Kerby, R. L., Dill-McFarland, K. A., Harding, S. J., Merluzzi, A. P., Johnson, S. C., ... & Bendlin, B. B. (2017). Gut microbiome alterations in Alzheimer's disease. *Scientific Reports*, *7*(1), 1. doi: 10.1038/s41598-017-13601-y.

Wallace, C. J., & Milev, R. (2017). The effects of probiotics on depressive symptoms in humans: a systematic review. *Annals of General Psychiatry*, *16*(1), 14. doi: 10.1186/s12991-017-0138-2.

Wang, X., Wang, B. R., Zhang, X. J., Xu, Z., Ding, Y. Q., Ju, G. (2002). Evidences for vagus nerve in maintenance of immune balance and transmission of immune information from gut to brain in STM-infected rats. *World Journal of Gastroenterology*, *8*(3), 540. doi: 10.3748/wjg.v8.i3.540.

Weisman, H., Qureshi, I. A., Leckman, J. F., Scahill, L., & Bloch, M. H. (2013). Systematic review: pharmacological treatment of tic disorders-efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neuroscience & Biobehavioral Reviews*, *37*(6), 1162. doi: 10.1016/j.neubiorev.2012.09.008.

Yamamura, S., Morishima, H., Kumano-go, T., Suganuma, N., Matsumoto, H., Adachi, H., ... & Takano, T. (2009). The effect of *Lactobacillus helveticus* fermented milk on sleep and health perception in elderly subjects. *European Journal of Clinical Nutrition*, *63*(1), 100. doi: 10.1038/sj.ejcn.1602898.

Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., ... & Hsiao, E. Y. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*, *161*(2), 264. doi: 10.1016/j.cell.2015.02.047.

Zhao, H., Shi, Y., Luo, X., Peng, L., Yang, Y., & Zou, L. (2017). The effect of fecal microbiota transplantation on a child with Tourette syndrome. *Case reports in Medicine*, *2017*. doi: 10.1155/2017/6165239.

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