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# Psychobiotics in daily food against psychiatric disorders

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**Psychobiotics are probiotics microorganisms that affect the central nervous system neurological functions of a host. The gut-brain-axis via immune-metabolic pathways balances the gastrointestinal function and improves the quality of life of hosts with psychiatric disorders. Gut microorganisms have been found to participate in the balance of various psychiatric disorders, including "Anxiety and Depression", "Alzheimer's disease", "Parkinson's disease", "Autism Spectrum Disorder" and "Tourette syndrome". Scientific evidence points to an association between gut microbial imbalance and psychiatric disorders. The microbiome-gut-brain axis is a target for treating psychiatric disorders using nutritional strategies, such as through the intake of probiotics. Here, we report the main effects of psychobiotic therapy against psychiatric disorders. In conclusion, psychobiotics showed considerable neurological benefits, which opens avenues for new scientific research *in vivo* towards treating psychiatric disorders.**

**Key words:** Probiotic food, microbiome-gut-brain axis, mental health.

## INTRODUCTION

The microbiome-gut-brain axis is one of the most important advances in the field of neuroscience and gastroenterology in the last times (Gill et al., 2006; Cryan et al., 2019). The gut-brain-axis via immune-metabolic pathways balance the gastrointestinal function and improve the quality of life of hosts with psychiatric disorders. Gut microorganisms have been found to participate in the balance of various psychiatric disorders (Turnbaugh et al., 2006; Sarkar et al., 2016; Cryan et al., 2019; Magalhães-Guedes, 2020). The host microbiota

profile is controlled by factors such as diets, genetics, sex and age. The gut microbiome is responsible for important functions in hosts health. In particular, gut dysbiosis is correlated with various disorders of the central nervous system. For example, low number of *Bifidobacterium* species and/or *Lactobacillus* species results in individuals with a high level of depressive disorder (Aizawa et al., 2016; Wallace and Milev, 2017).

The microbiome-gut-brain axis is involved in the neuropathology of psychiatric disorders (Carabotti et al.,

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2015; Evrensel and Ceylan, 2015; Sucksdorff et al., 2015; Cenit et al., 2017; Magalhães-Guedes, 2020). The scientific evidence came from the animal and human studies which compared gut microbiome composition of neurodepressed and non-neurodepressed animals/humans (Foster et al., 2017; Inserra et al., 2018; Partrick et al., 2018; Papalini et al., 2019). Nutritional therapies have been made to re-establish the gut microbiome in neurodepressed patients to alleviate symptoms.

New strains of probiotic microorganisms are important focus of future studies to elucidate their psychobiotic potential, particularly in psychiatric disorders. In this review, we report the main effects of psychobiotic therapy against various psychiatric disorders, including "Anxiety and Depression", "Alzheimer's disease", "Parkinson's disease", "Autism Spectrum Disorder" and "Tourette syndrome".

## METHODOLOGY

A bibliographic research study was conducted to collect data and information on psychobiotics against psychiatric disorders. The research sites accessed were: e-books, theses and the Scielo database, Google Scholar, Medline, Pubmed, Science Direct and CAPES periodical portal and the virtual health/food library. The index terms used for single searches were psychobiotics, probiotics, psychiatric disorders, anxiety and depression, Alzheimer's disease, Parkinson's disease, autism spectrum disorder, Tourette syndrome, microbiome-gut-brain axis and mental health. Papers that did not match the searched words were excluded. The exclusion criterion also applies to articles that after reading that did not refer to the main objective of the study. In total, 50 articles were recruited and 3 scientific articles published on government research website: <https://ClinicalTrials.gov>.

## RESULTS

### Psychobiotics

Psychobiotics is a term used in preliminary research to refer to live microorganisms that, when ingested in appropriate amounts, might confer a mental health benefit by affecting microbiota of the host organism (Dinan et al., 2013; Ross, 2017; Sucksdorff et al., 2015; Cenit et al., 2017; Magalhães-Guedes, 2020; Magalhães-Guedes et al., 2020). The scientific evidence came from the animal and human studies which compared gut microbiome composition of neurodepressed and non-neurodepressed animals/humans (Sarkar et al., 2016; Foster et al., 2017; Inserra et al., 2018; Partrick et al., 2018; Papalini et al., 2019). Psychobiotic microorganisms can regulate proteins brain-derived, influencing the cognitive functions and memory (Sudo et al., 2004; Lu et al., 2008; Martinowich and Lu, 2008; Silverman and Sternberg, 2012; Foster et al., 2017; Inserra et al., 2018; Partrick et al., 2018; Papalini et al., 2019).

In experimental probiotic psychobiotics, the bacteria

most commonly used are Gram-positive bacteria, such as *Bifidobacterium* and *Lactobacillus* families, as these do not contain lipopolysaccharide chains, reducing the likelihood of an immunological response (Silverman and Sternberg, 2012; O'Mahony et al., 2015; Roshchina, 2016).

The gut microbiota is modified and evolves from birth, moving from an immature state in newborns during childhood to a more complex and diverse ecosystem in adulthood. Gut microbial imbalance can have negative consequences on the health of the host, leading to gastrointestinal, immunological and neurological disorders. In this context, different strains of psychobiotics have been successfully used as food to improve the health of the host by modulating the gut microbial ecosystem and improving the hosts gut behavior (Hemarajata and Versalovic, 2013; Sucksdorff et al., 2015; Cenit et al., 2017; Ross, 2017; Magalhães-Guedes, 2020).

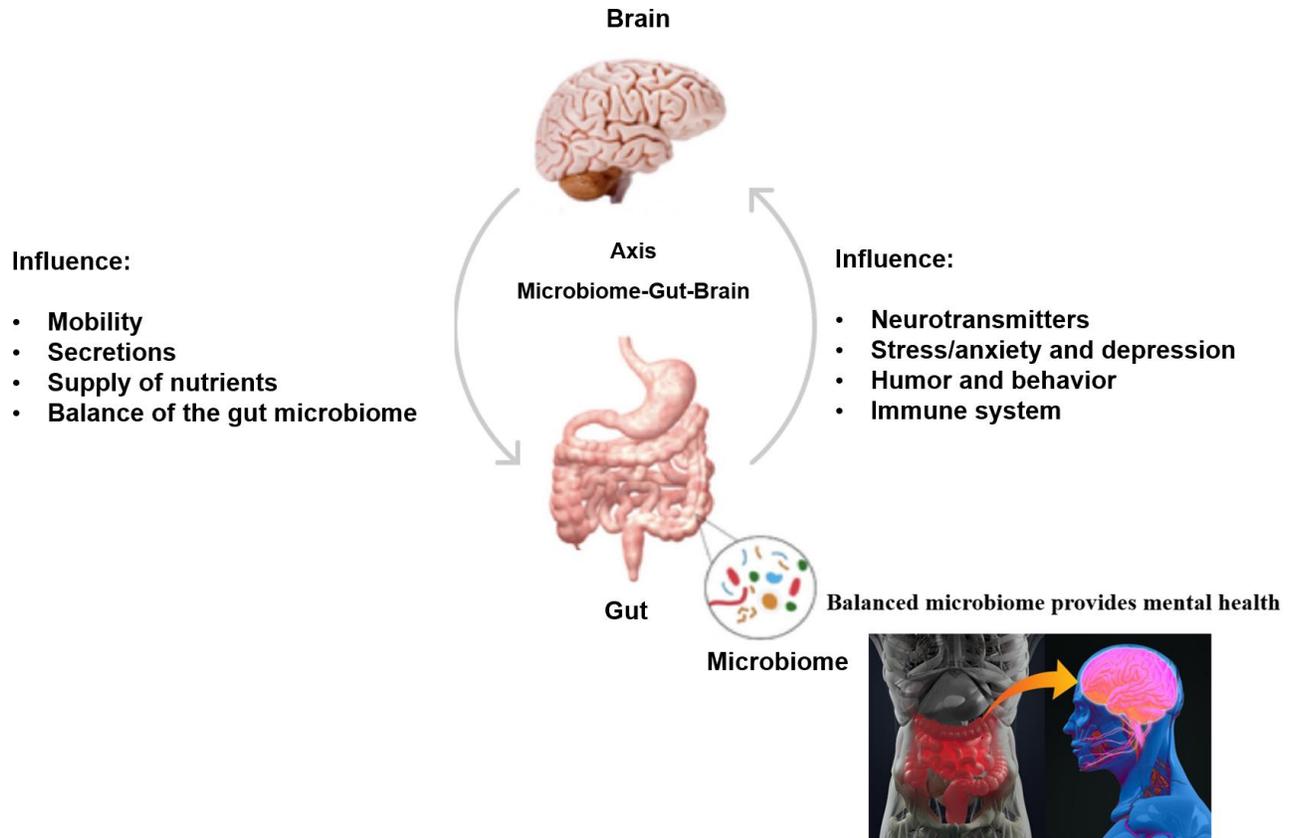
The combination of a diet probiotica and physical activity have been shown to affect behavior and mood, in part by modifying the functions of the microbiome-gut-brain axis, keeping the host health relatively stable (Magalhães-Guedes, 2020).

### Gut-brain axis

According to previous studies, the interest in the connection between gut health and psychological well-being received the name "Axis of the Microbiome-Gut-Brain", which is a bidirectional regulatory system involving the brain, the central nervous system and the gut (Konturek et al., 2011; Hemarajata and Versalovic, 2013; Sucksdorff et al., 2015; Cenit et al., 2017; Ross, 2017; Magalhães-Guedes, 2020).

The gut and brain send and receive information through the enteric nervous system, through neural pathways such as the efferent sympathetic system and the afferent vagal nerve, as well as through the bloodstream (Bercik et al., 2012). The enteric nervous system also influences the functions of the gastrointestinal tract, pancreas, gallbladder, endocrine function and nervous system, as well in the regulation of the host health (Bercik et al., 2012).

Although the interactions of the gut-brain and microbiome are multifactorial and not well understood. The gut-brain axis system functions as a communication channel between the gut microbiome and the brain (Konturek et al., 2011). The gut-brain axis provides a pathway of bidirectional communication that can cause several pathophysiological consequences if there is deregulation. This axis is regulated at the neural, hormonal and immune levels. Modulation of the function of the gut-brain axis is associated with specific changes in the response to stress and behavior in general (Konturek et al., 2011). Figure 1 shows the



**Figure 1.** System “Microbiome-Gut-Brain Axis”.

“Microbiome-Gut-Brain Axis” mechanism.

Several afferent or efferent pathways are connected in the Microbiome-Gut-Brain axis. Antibiotics, environmental factors infectious agents, neurotransmitters, fibers and cytosines transmit information about the gut microbiome state to the central nervous system. Such interactions seem to influence the pathogenesis of a series of disorders in which inflammation is implicated as mood disorder, stress and depression (Petra et al., 2015; Cryan et al., 2019).

## Psychobiotics action against psychiatric disorders

### *Anxiety and depression*

A healthy mind represents a mental status of physical and neurological well-being (Dinan et al., 2013). They report that the ingestion of psychobiotics microorganisms may require a precision to address anxiety and depression symptoms. Scientific research has shown that psychobiotics have a promising effect on depression, anxiety and stress (Dinan et al., 2013). Several probiotic microorganisms strains have been reported as psychobiotics according to animal (mice) studies (Liu et

al., 2016). Regular consumption of strains of *Lactobacillus* reduced anxiety and depression symptoms in mice. *Lactobacillus* significantly decreased inflammation and corticosterone levels. Consumption of the *Lactobacillus* strains significantly increased the levels of dopamine and serotonin in the prefrontal and striated cortex of mice (Liu et al., 2016). Dairy *Lactobacillus* consumption reduced the anxiety, depression and intestinal dysbiosis in mice. In addition, *Lactobacillus* strains increased levels of serotonin and norepinephrine in the brain (Bravo et al., 2011; Liang et al., 2015). Using the *Bifidobacterium* strains daily, it was found that the stress, depression and anxiety symptoms have been reduced (Savignac et al., 2014). Regular consumption of the *Bifidobacterium longum* was effective in treating anxiety symptoms (Savignac et al., 2014).

In addition to studies with promising animals (mice), several studies have found positive effects of probiotics microorganisms on psychological health in humans. Healthy volunteers who were given *Bifidobacterium* strain for four weeks exhibited reduced anxiety and better mood (Allen et al., 2016).

Psychobiotics microorganisms were administered to a population of  $10^9$  CFU/mL in 16, 21 and 28 days, observing the reduction in levels of anxiety and

depression (Mohammadi et al., 2016). Petrochemical workers using both psychobiotics (probiotic capsules and yoghurts) exhibited better health parameters, assessing anxiety and depression (Mohammadi et al., 2016).

Some clinical studies have looked at the effects of some probiotic supplements (*Lactobacillus plantarum* PS128, *Lactobacillus plantarum* 299, *Lactobacillus rhamnosus* GG, Probio'Stick and Vivomixx®) in combating depression and anxiety (Mohammadi et al., 2016). These studies evaluated in humans the state of stress and mood. Approximately, 95% of the serotonin formed is derived from gut enterochromaffin cells and neurons, which is associated with the gut-brain axis regulation. In addition, serotonin brain pathways are involved in the regulation of mood (Savignac et al., 2014; Mohammadi et al., 2016; Cryan et al., 2019).

### **Alzheimer's disease**

Alzheimer's disease is a chronic neurodegenerative disorder characterized by characterized by loss of cognitive movements and memory (Kumar et al., 2015). Studies investigated the effect of multiple microbial strains, such as *Lactobacillus* and *Bifidobacterium* strains on an animal model (mice) with Alzheimer's. The total counts of *Lactobacillus* and *Bifidobacterium* strains were increased and Coliform strain was decreased in the stool of mice after regular consumption of these probiotic strains. Furthermore, probiotic microorganisms supplementation improved learning deficits in Alzheimer's disease mice compared with control mice (Athari et al., 2018).

One randomized, double-blind, and controlled clinical trial found that consumption of probiotic-fermented milk improved the health of mice with Alzheimer's disease (Akbari et al., 2016). Based on the findings from mice studies, probiotics improved the cognitive movements and memory of the control mice (Musa et al., 2017; Athari et al., 2018).

There is scientific evidence that there is a direct biochemical link between the brain and the digestive system, but there is still no complete data on the subject. Alzheimer's acts directly on a neuroinflammation, in insulin resistance that can cause diabetic processes and also alter the metabolism of lipids. However, probiotics can reduce this influence by acting directly on these disorders (Musa et al., 2017; Agahi et al., 2018; Athari et al., 2018).

### **Parkinson's disease**

Parkinson's disease is a neuropsychiatric disorder that reduces the neurological health of two percent of the elderly population (Barichella et al., 2009). Gut dysbiosis is a common symptom in elderly people with Parkinson's disease (Barichella et al., 2009).

The use of probiotics microorganismis in patients with Parkinson's disease diet has been previously studied. Studies have found that patients with Parkinson's disease who were using probiotic microorganisms exhibited improvement in gut dysbiosis (Barichella et al., 2016). The clinical studies of the probiotics microorganisms consumption by patients with Parkinson's disease have been focused on gut-brain axis function (Barichella et al., 2009, 2016; TPCPD, 2020). Only one recent study reported that probiotics microorganisms consumption improves the movement of the upper limb (arm) of patients with Parkinson's disease (Tamtaji et al., 2018).

### **Autism spectrum disorder**

Autism spectrum disorder, a neurodevelopmental disorder, is characterized by deficits in social interactions across multiple contexts and levels, accompanied by behavior and repetitive patterns of interests, and/or activities (Wang et al., 2011; Li-Hao et al., 2019). Patients with autism spectrum disorder frequently experience gut dysbiosis (diarrhea or constipation) (Wang et al., 2011). Recent studies have shown that probiotics microorganisms could improve the gastrointestinal disorders and even the autism spectrum disorder-related symptoms in diagnosed patients (PQLASD, 2020). The effects of some multiple commercial strain/probiotic products on patients with autism spectrum disorder have been investigated. In 2016 and 2017, the effects of "Visbiome (product containing eight probiotic strains)" on gut dysbiosis symptoms in children with autism spectrum disorder were investigated (PQLASD, 2020). Satisfactory results have been achieved (PQLASD, 2020). Multiple microbial strains or single microbial strains of probiotics (mainly bacteria from the genera *Lactobacillus* and *Bifidobacterium*) were reported to exhibit healthy effects on children with autism spectrum disorder (Parracho et al., 2010; Shaaban et al., 2018).

### **Tourette syndrome**

Tourette syndrome is a neurological disorder that are typically first observed in childhood (Rampello et al., 2006; Li-Hao et al., 2019). It is characterized by multiple movement (motor) tics and at least one vocal (phonic) tic. Common tics are blinking, coughing, throat clearing, sniffing, and facial movements. These are typically preceded by an unwanted urge or sensation in the affected muscles, can sometimes be suppressed temporarily, and characteristically change in location, strength, and frequency (Li-Hao et al., 2019).

Tourette syndrome is at the more severe end of a spectrum of "tic disorders". The clinical treatments of Tourette syndrome include behavioral treatments, antipsychotics, and deep brain stimulation (Murphy et al.,

2013; Weisman et al., 2013; Li-Hao et al., 2019). According to one recent study, consumption of probiotic microorganisms strains ameliorates Tourette syndrome in eight weeks after the treatment daily consumption (Zhao et al., 2017).

Randomized, double-blind, placebo-controlled clinical trial was conducted to elucidate the effect of strains of probiotic microorganisms as psychobiotics in Tourette's syndrome (TRPMD, 2020). The primary studies showed satisfactory results after two months of intervention of strains of probiotic microorganisms (TRPMD, 2020).

## DISCUSSION

Scientific studies reported in this review provided evidence of the effects of psychobiotics (probiotic microorganisms) on psychiatric disorders, including "Anxiety and Depression" (Liu et al., 2016), "Alzheimer's disease" (Athari et al., 2018), "Parkinson's disease", "Autism Spectrum Disorder" (Shaaban et al., 2018) and "Tourette syndrome" (Zhao et al., 2017).

Scientific evidence points to an association between gut microbial imbalance and psychiatric disorders (Konturek et al., 2011; Hemarajata and Versalovic, 2013; Sucksdorff et al., 2015; Cenit et al., 2017; Ross, 2017; Magalhães-Guedes, 2020). Some of the single or multiple microbial strains can improve the functions of the central nervous system, including mood, anxiety, stress and depression (PQLASD, 2020). In addition, psychobiotic treatments have shown promising effects on the balance of the gut-brain axis (Konturek et al., 2011; Hemarajata and Versalovic, 2013; Sucksdorff et al., 2015; Cenit et al., 2017; Ross, 2017; Magalhães-Guedes, 2020). Thus, psychobiotic treatments can be a promising strategy to improve the quality of life of people with various mental imbalances.

Therefore, the use of probiotic microorganisms is recommended to maintain mental and emotional balance. Regardless of the diagnosis of physical or emotional disorders, we recommend daily consumption of probiotic microorganisms. The benefits to your health and well-being are immense.

## Conclusion

In this review, the main effects of psychobiotic therapy against psychiatric disorders was reported. In conclusion, psychobiotics microorganisms showed considerable neurological benefits, which opens avenues for new scientific research towards treating psychiatric disorders, for example the elaboration and *in vivo* analysis of "psychobiotic foods" for insertion in the market.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

## REFERENCES

- Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, Ota M, Koga N, Hattori K, Kunugi H (2016). Possible association of Bifidobacterium and *Lactobacillus* in the intestine microbiota of patients with major depressive disorder. *Journal of Affective Disorders* 202:254e7.
- Agahi A, Hamidi GA, Daneshvar R, Hamdieh M, Soheili M, Alinaghypour A, Taba SME, Salami M (2018). Does severity of Alzheimer's disease contribute to its responsiveness to modifying intestine microbiota? A double blind clinical trial. *Frontiers in Neurology* 18:9:662.
- Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind and controlled trial. *Frontiers in Aging Neuroscience* 8:256.
- Allen AP, Hutch W, Borre YE, Kennedy PJ, Temko A, Boylan G, Murphy E, Cryan JF, Dinan TG, Clarke G (2016). *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Translational Psychiatry* 6(11):e939.
- Athari NA, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, Sharifzadeh M, Vafa M (2018). Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in beta-amyloid (1-42) injected rats. *Applied Physiology Nutrition and Metabolism* 43:718-726.
- Barichella M, Cereda E, Pezzoli G (2009). Major nutritional issues in the management of Parkinson's disease. *Movement Disorders* 24:1881-1892.
- Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, Pinelli G, Cesari I, Faierman AS, Caccialanza R, Pezzoli G, Cereda E (2016). Probiotics and prebiotic fiber for constipation associated with Parkinson disease: an RCT. *Neurology* 87(12):1274-1280.
- Bercik P, Collins SM, Verdu EF (2012). Microbes and the intestine-brain axis. *Neurogastroenterol Motility* 24(5):405-413.
- Bravo JÁ, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF (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 of the United States of America* 108(38):16050-16055.
- Carabotti M, Scirocco A, Maselli MA, Severi C (2015). The intestine-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology* 28:203-209.
- Cenit MC, Nuevo IC, Codoner-Franch P, Dinan TG, Sanz Y (2017). Intestine microbiota and attention deficit hyperactivity disorder: New perspectives for a challenging condition. *European Child and Adolescent Psychiatry* 26:1081-1092.
- Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV (2019). The microbiota-gut-brain axis. *Physiological Reviews* 99:1877-2013.
- Dinan TG, Stanton C, Cryan JF (2013). Psychobiotics: A novel class of psychotropic. *Biological Psychiatry* 74:720-726.
- Evrensel A, Ceylan ME (2015). The gut-brain Axis: the missing link in depression. *Clinical psychopharmacology and neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology* 13(3):239e44.
- Foster JA, Rinaman L, Cryan JF (2017). Stress and the gut-brain axis: regulation by the microbiome. *Neurobiology of Stress* 7:124-136.
- Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE (2006). Metagenomic analysis of the human distal intestine microbiome. *Science* 312:1355-1359.
- Hemarajata P, Versalovic J (2013). Effects of probiotics on intestine microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic Advances in Gastroenterology* 6(1).
- Inserra A, Rogers GB, Licinio J, Wong ML (2018). The microbiota-inflammation hypothesis of major depression. *Bioessays* 40(9):1800027.
- Konturek PC, Brzozowski T, Konturek SJ (2011). Stress and the intestine: Pathophysiology, clinical consequences, diagnostic

- approach, and treatment options. *Journal of Physiology and Pharmacology* 62(6):591–599.
- Kumar A, Singh A, Ekavali A (2015). A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacological Reports* 67:195e203.
- Liang S, Wang T, Hu X, Luo J, Li W, Wu X, Duan Y, Jin F (2015). Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. *Neuroscience* 310:561-577.
- Li-Hao C, Yen-Wenn L, Chien-Chen W, Sabrina W, Ying-Chieh T (2019). Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. *Journal of Food and Drug Analysis* 27(3):632-648.
- Liu YW, Liu WH, Wu CC, Juan YC, Wu YC, Tsai HP, Wang S, Tsai YC (2016). Psychotropic effects of *Lactobacillus plantarum* PS128 in early life-stressed and naive adult mice. *Brain Research* 1631:1-12.
- 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* 89:312-323.
- Magalhães-Guedes KT (2020). The Dialogue between the Intestine-brain Axis: What is the Role of Probiotics?. *Asian Food Science Journal* 14:23-27.
- Magalhães-Guedes KT, Anunciação TA, Nascimento ASM (2020). Psicobióticos na saúde mental contra transtorno da ansiedade e depressão. In: Luis HAC, Thiago TP, Silvia AO (Org.). *Ciências da Saúde: Campo Promissor em Pesquisa* 7. 1ed.Ponta Grossa - PR: Atena Editora 1:105-112.
- Martinowich K, Lu B (2008). Interaction between BDNF and serotonin: Role in mood disorders. *Neuropsychopharmacology* 33:73-83.
- Mohammadi AA, Jazayeri S, Khoravi-Darani K, Solati Z, Mohammadpour N, Asemi Z, Djalali M, Tehrani-Doost M, Hosseini M, 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):387-395.
- Murphy TK, Lewin AB, Storch EA, Stock S (2013). American Academy of Child and Adolescent Psychiatry Committee on Quality I. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 13(52):1341-1359.
- Musa NH, Mani V, Lim SM, Vidyadaran S, Abdul Majeed AB, Ramasamy K (2017). Lactobacilli-fermented cow's milk attenuated lipopolysaccharide-induced neuroinflammation and memory impairment in vitro and in vivo. *Journal of Dairy Research* 84:488-495.
- O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF (2015). Serotonin, tryptophan metabolism and the brain-intestine-microbiome axis. *Behavioural Brain Research* 277:32-48.
- Papalini S, Michels F, Kohn N, Wegman J, Van Hemert S, Roelofs K, Arias-Vasquez A, Aarts E (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of Stress* 10:100141.
- Parracho HMRT, Gibson GR, Knott F, Bosscher D, Kleerebezem M, McCartney AL (2010). A double-blind, placebocontrolled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. *International Journal of Probiotics and Prebiotics* 5:69-74.
- Petra AI, Panagiotidou S, Hatzigelaki E, Stewart JM, Conti P, Theoharides TC (2015). Gut-microbiota-brain axis and effect on neuropsychiatric disorders with suspected immune dysregulation. *Clinical Therapeutics* 37(5):984-995.
- Patrick KA, Chassaing B, Beach LQ, McCann KE, Gewirtz AT, Huhman KL (2018). Acute and repeated exposure to social stress reduces gut microbiota diversity in Syrian hamsters. *Behavioural Brain Research* 345:39-48.
- PQLASD (2020). Probiotics for Quality of Life in Autism Spectrum Disorders. <https://ClinicalTrials.gov/show/NCT02903030>.
- Rampello L, Alvano A, Battaglia G, Bruno V, Raffaele R, Nicoletti F (2006). Tic disorders: From pathophysiology to treatment. *Journal of Neurology* 253:1-15.
- Ross SM (2017). Microbiota in Neuropsychiatry, Part 3 Psychobiotics as Modulators of Mood Disorders. *Holistic Nursing Practice* 31(4):270-273.
- Roshchina VV (2016). New trends and perspectives in the evolution of neurotransmitters in microbial, plant, and animal cells. *Advances in Experimental Medicine and Biology* 874:25-77.
- Savignac HM, Kiely B, Dinan TG, Cryan JF (2014). Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Journal of Neurogastroenterology and Motility* 26:1615-1627.
- Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ (2016). Psychobiotics and the manipulation of bacteria-intestine-brain signals. *Trends in Neurosciences* 39:763-781.
- Shaaban SY, El Gendy YG, Mehanna NS, El-Senousy WM, El-Feki HSA, Saad K, El-Asheer OM (2018). The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. *Nutritional Neuroscience* 21(9):676-681.
- Silverman MN, Sternberg EM (2012). Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Annals of the New York Academy of Sciences* 1261:55-63.
- Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelson P, Gissler M, Sourander A (2015). Preterm birth and poor fetal growth as risk factors of attention-deficit/hyperactivity disorder. *Pediatrics* 136(3):599-608.
- Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y (2004). Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *Journal of Physiology* 558:263-275.
- Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, Kouchaki E, Bahmani F, Borzabadi S, Oryan S, Mafi A, Asemi Z (2018). Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clinical Nutrition* 38(3):1031-1035.
- TPCPD (2020). Trial of Probiotics for Constipation in Parkinson's Disease. <https://ClinicalTrials.gov/show/NCT03377322>.
- TRPMD (2020). The Role of Probiotics PS128 in Movement Disorders. <https://ClinicalTrials.gov/show/NCT03259971>.
- Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006). An obesity-associated intestine microbiome with increased capacity for energy harvest. *Nature* 444:1027-1031.
- Wallace CJK, Milev R (2017). The effects of probiotics on depressive symptoms in humans: a systematic review. *Annals of General Psychiatry* 16-14.
- Wang LW, Tancredi DJ, Thomas DW (2011). The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. *Journal of Developmental and Behavioral Pediatrics* 32:351-360.
- Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH (2013). Systematic review: pharmacological treatment of tic disorders—efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neuroscience and Biobehavioral Reviews* 37:1162-1171.
- 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* 2017:6165239.