

Review Article

Probiotics in human mental health and diseases-A mini-review

Bhagavathi Sundaram Sivamaruthi¹, Mani Iyer Prasanth², Periyannaina Kesika¹,
Chaiyavat Chaiyasut^{1*}

¹Innovation Center for Holistic Health, Nutraceuticals, and Cosmeceuticals, Faculty of Pharmacy, Chiang Mai University, Chiang Mai-50200, ²Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand

*For correspondence: **Email:** chaiyavat@gmail.com; **Tel:** +66-53944340

Sent for review: 25 October 2018

Revised accepted: 23 March 2019

Abstract

In humans, cognitive functions are controlled by the central nervous system, which is controlled by the brain. Any damage to the neuronal system causes serious impairment to the host as it may lead to neurodegenerative diseases like Parkinson's, Alzheimer's, autism and epilepsy. The physical and mental health of an individual is associated with food habits and brain health. The hypothalamus is the region of the brain that initiates a response to different types of stress. However, recent findings have revealed that food play a major role in regulating stress and mental health. In this regard, probiotics are beneficial microbes that are claimed to offer health benefits when consumed in adequate quantities. Probiotics alter the gut microbial composition in a positive way. Several in vitro, in vivo and pre-clinical studies have been conducted to determine the effects of probiotics or probiotic based food supplementation on the cognitive function of model system and human volunteers. Most of the studies suggest that the consumption of probiotic formulations improves cognitive function, stress management, and decision-making. This paper reviews recent findings regarding the influence of probiotic supplementation on cognitive function, especially in human subjects. The role of probiotics in maintaining healthy gut microbiota and detailed outcomes of clinical trials are here reported for easy understanding of the concept. However, more studies involving clinical trials are still required in the field of probiotics and cognitive function.

Keywords: Probiotics, Stress, Anxiety, Cognition, Microbiome, Brain health

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Probiotics are living microbes that boost the healthy life of the host's system, when supplemented appropriately. Probiotics exhibit health promoting properties by improving the immune system, supplying antioxidants and

improving mental health. Fermented foods, like yogurt and kefir, are the major sources of probiotics as well as certain fermented vegetables, which are available as dietary supplements in the market [1]. They reduce the side effects of gastrointestinal tract diseases, antibiotic treatment-related symptoms [2], and

also exhibit several health benefits [3-6].

The use of probiotics in infant formulas commenced recently. In this regard, the supplementation of specific *Bifidobacterium* or *Streptococcus* strains was found to exhibit a significant reduction in cases of gastrointestinal infections, without altering the normal growth and development in infants [7].

Probiotics need nutrients for their survival, reproduction, and existence. These nutrients are termed prebiotics, and the probiotic microbes feed on them. Plant based foods, such as fruits, vegetables, and nuts, are the sources of probiotic dietary fiber [1]. Prebiotic-mediated growth and development of probiotics (*Lactobacillus* and *Bifidobacterium* genera) show several beneficial effects on host system [8].

In humans, cognitive functions are controlled by the central nervous system, which is controlled by the brain. Any damage in the brain or nervous system may lead to neurodegenerative diseases like Parkinson's, Alzheimer's, autism and epilepsy. A recent study showed that selective modifications in alpha-synuclein protein, which is abundantly present in erythrocytes, can act as a biomarker for Parkinson's disease [9].

The physical and mental health of an individual is controlled by both the brain and the habitat. The hypothalamic region of the brain responds to different types of stress. However, recent studies have shown that feeding behavior too could play a role in regulating stress and mental health [10]. Accordingly, the intake of probiotics might have a beneficial effect on mental health [10].

The present review focuses on the role of probiotics in mental health and diseases. Researchers now believe that the complex bidirectional communication that occurs between the brain and gut microbiota (GM) could be a new way forward in determining therapies for mental illness [11]. Clinical studies are required for further confirmation before being implemented in the field of pharmacy. However, studies with several animal models have been reported revealing the specific role of GM in mediating mental illnesses including anxiety and trauma [12]. The research articles and reviews were collected from scientific repositories, including Scopus, PubMed, and Google Scholar, using the keywords "Probiotics and cognition", "Probiotics and microbiome", as well as "Probiotics and brain function". The relevant documents were used for the preparation of the manuscript without any chronological restrictions.

INFLUENCE OF MICROBIOME ON HUMAN HEALTH

Several bacteria are known to cause adverse effects to mankind. The prevalence of these bacteria causes damage to the overall health and cognitive functions of an individual. These infectious microbes damage the normal microbial flora residing inside the host, causing an imbalance between the beneficial bacteria and pathogenic bacteria, which affects the host's immune system. One of the most prevalent bacterial infections, urinary tract infections (UTIs), is caused by different pathogens among which, *Escherichia coli* is the most prominent. *Lactobacillus*, a well-known probiotic species, has been observed in the vaginal microbiome of healthy individuals. In this regard, administration of probiotics (*Lactobacillus*) could be considered as an effective treatment strategy against UTIs [13].

It has been known for ages that breast milk is the complete food for infants since it contains enough nutrients that will develop the immune system of infants. Moreover, it helps in the inoculation and development of the GM [14]. The establishment of the GM starts during early childhood. As age increases, the diversity of the GM also increases and becomes stable during adulthood. The GM is dominated mostly by Firmicutes and Bacteroidetes during the adult stage [15].

Infants fed with breast milk have GM dominated by *Bifidobacterium* followed by *Bacteroides* [16]. The growth and development of *Bifidobacterium* [16] and *Bacteroides* [16] in breast fed infants are promoted by the oligosaccharides present in breast milk, which act as prebiotics [17]. Obesity, diabetes and intestinal dysbiosis in a mother during pregnancy could increase the risk for neuropsychiatric disorders [18] and sex-specific behavior [19] in the offspring. Prenatal and postnatal maternal oral probiotic therapy could be considered as an effective treatment method to prevent allergy [20], and atopic dermatitis [5,20].

Different factors like change in diet, change in habitat, illness and consumption of antibiotics, can cause an imbalance in GM [21], which could be regained over time. However, chronic and prolonged conditions can lead to serious issues ranging from obesity, allergies, psychiatric, and behavioral problems [1,21,22]. It has been observed that 95 % of serotonin is synthesized in the gut [23] and the GM regulates the biosynthesis of serotonin [24].

The GM is also known to regulate the permeability of blood-brain barrier [25]. Thus, imbalance in the GM could adversely affect the brain and nervous system leading to depression [26], and neurodegenerative diseases like Parkinson's and Alzheimer's [2]. A recent study reported that germ-free mice showed increased permeability of blood-brain barrier [25]. The study also revealed that reduced permeability of blood-brain barrier and increased expression of tight junction proteins were observed in germ-free mice when exposed to the GM of normal mice [25]. The intervention of *Lactobacillus* species (*L. helveticus* and *L. rhamnosus*) have been found to prevent memory dysfunction in *Citrobacter rodentium* infected mice (C57BL/6) by improving the expression of brain-derived neurotrophic factor (BDNF) [27]. The reduced expression of BDNF has been reported in the blood and brain of Alzheimer's patients [28].

INFLUENCE OF PROBIOTICS ON MENTAL HEALTH

Several studies have reported that the GM play a significant role in the emotion and behavior of an individual, and it could be of considerable importance in mental health treatment. The stress mediated physiological effects in the gut, such as nausea, and bouts of diarrhea, thereby having a vital impact on the equilibrium of the GM [29]. A new group of probiotics, named psychobiotics are used to improve the cognitive functions in patients with psychiatric illness [30]. Many distinct gut microbial species produce diverse neuromolecules involved in mood regulation, which affects host physiology. Different species of *Bifidobacterium* and *Lactobacillus* generate gamma-aminobutyric acid (GABA), while *Enterococcus*, *Escherichia*, *Streptococcus*, and *Candida* species synthesize serotonin and *Bacillus* species produce dopamine [31].

In vivo effect

In a recent study, researchers found that a commensal *L. reuteri* strain restores the normal social behavior and oxytocin levels in mice with maternal-high-fat-diet mediated dysbiosis [32]. Periodic maternal separation induces stress in rats, which reduces the diversity of the gastrointestinal microbiome when compared with the control [33].

In a study, BALB/c mice and NIH Swiss mice were compared by switching the GM between them. Naturally, BALB/c mice are more nervous, whereas NIH Swiss mice are much more exploratory in nature. Interestingly, the BALB

mice exhibited some behavior of Swiss peers, like increased exploratory behavior and BDNF expression in the hippocampus. Similarly, Swiss mice also demonstrated anxiety and other behavioral features of their microbiome donors [34]. However, the changes were not permanent in nature. Nonetheless, this study [34] revealed that alterations in GM can have a direct effect on the behavior and brain. These findings highlighted the bi-directional communication between the GM and the brain, which could be termed as "second" brain [29].

Clinical trials

A double-blind, placebo-controlled, randomized study using different species of probiotics (*B. longum* R0175 and *L. helveticus* R0052) showed beneficial effects, such as reducing the levels of anger-hostility, depression, and somatization in healthy human volunteers [35].

The consumption of yogurt containing *L. casei* Shirota improved the mood of healthy individuals [36]. Another similar study reported that a group of forty healthy young adults showed significant reduction in overall cognitive reactivity to depression as well as ruminative and aggressive thoughts after consuming a probiotic mixture (Ecologic@barrier) for 4 weeks [37]. Consumption of probiotic supplement (*B. bifidum*, *L. casei*, and *L. acidophilus*) significantly decreased the Beck Depression Inventory (BDI) scores and improved the mood as well as overall symptoms in patients diagnosed with depression [38]. In another study, the intensity of pain caused by functional abdominal pain and irritable bowel syndrome in children were reduced by the administration of *L. reuteri* DSM 17938 [39].

The intervention of *L. acidophilus* reduced the concentration of D-arabinitol and the ratio of D-arabinitol to L-arabinitol in the urine of 22 autism patients; it also improved their ability to follow directions [40]. The consumption of a probiotic mixture (*B. bifidum*, *B. longum*, *L. delbrueckii*, *L. casei*, and *L. acidophilus*) along with the immunomodulator Del-Immune V (*L. rhamnosus* V lysate) reduced the severity of autism in 33 children [41].

A study using the mouse model of early prenatal stress showed changes in the vaginal microbiome; the changes are associated with the shift in the abundance of *Lactobacillus*, which causes alterations in the metabolic profiles of the gut and brain of the offspring [42].

However, probiotics were also found to decrease anxiety and stress levels in subjects under

Table 1: Role of probiotics in mental health and diseases: Results from representative clinical studies

S/N	Intervention/ Supplement	Subject	Duration	Results	Reference
1	<i>Bifidobacterium longum</i> R0175 and <i>Lactobacillus helveticus</i> R0052	Healthy human volunteers	30 days	↓ Anxiety and depression-related behaviors.	[35]
2	<i>L. casei</i>	Healthy human volunteers	3 weeks	Improved the mood	[36]
3	<i>L. salivarius</i> W24, <i>L. brevis</i> W63, <i>B. bifidum</i> W23, <i>L. casei</i> W56, <i>B. lactis</i> W52, <i>L. acidophilus</i> W37, and <i>Lactococcus lactis</i>	Healthy young adults	4 weeks	↓ Negative thoughts linked with sad mood. ↓ Rumination and aggressive thoughts.	[37]
4	<i>B. bifidum</i> , <i>L. casei</i> and <i>L. acidophilus</i>	Patients with major depressive disorder	8 weeks	↓ Beck Depression Inventory total scores ↑ Plasma total glutathione level	[38]
5	<i>L. reuteri</i> DSM 17938	Children with functional abdominal pain and irritable bowel syndrome	4 months	↓ The severity and frequency of functional abdominal pain.	[39]
6	<i>L. acidophilus</i> Rosell-11	Autistic children	2 months	↓ D-arabinitol concentration and the ratio of D-arabinitol to L-arabinitol	[40]
7	<i>B. bifidum</i> , <i>B. longum</i> , <i>L. delbrueckii</i> , <i>L. casei</i> , and <i>L. acidophilus</i>	Autistic children	21 days	↓ Severity of autism	[41]
8	<i>L. casei</i> DN-114001	Academic student	6 weeks	↓ Stress and anxiety associated with exam stress	[43]
9	<i>L. helveticus</i> and <i>B. longum</i>	Patients who taking psychotropic medications	8 weeks	No significant changes in psychological outcome measures	[44]
10	<i>L. helveticus</i> IDCC3801	Healthy older adults	12 weeks	↑ Cognitive function	[45]

Abbreviations: ↓, Decreased; ↑, Increased

academic examination stress [43]. A recent study reported that consumption of probiotics (*B. longum* and *L. helveticus*) showed no significant beneficial effects in treating mood disorders [44]. Fermented milk containing *L. helveticus* IDCC3801, which was observed to improve cognitive function in healthy elderly people, had no effect on stress or geriatric depression symptoms [45] (Table 1, Figure 1).

CONCLUSION AND FUTURE PERSPECTIVES

The probiotics used in the food industry are the traditional probiotics that have been considered safe for decades. Next-generation probiotics are novel microbes the human GM that are associated with health and have no history of

usage in the food industry [46]. New and novel techniques are being implemented to determine new probiotics with better activities. Through various pre-clinical trials, new probiotics, such as *Clostridium* clusters, *Bacteroides uniformis*, *Akkermansia muciniphila*, *Faecalibacterium prausnitzii* [47], *Bacteroides fragilis* [48], and *Eubacterium hallii* [49] that have health beneficial effects have been developed and are considered as next-generation probiotics [50]. Probiotic based treatment has a wide industrial application since it can provide a better way to manage disease resistance [50]. However, the safety, stability and shelf life of the next-generation probiotics must be carefully studied to ensure their health promoting properties.

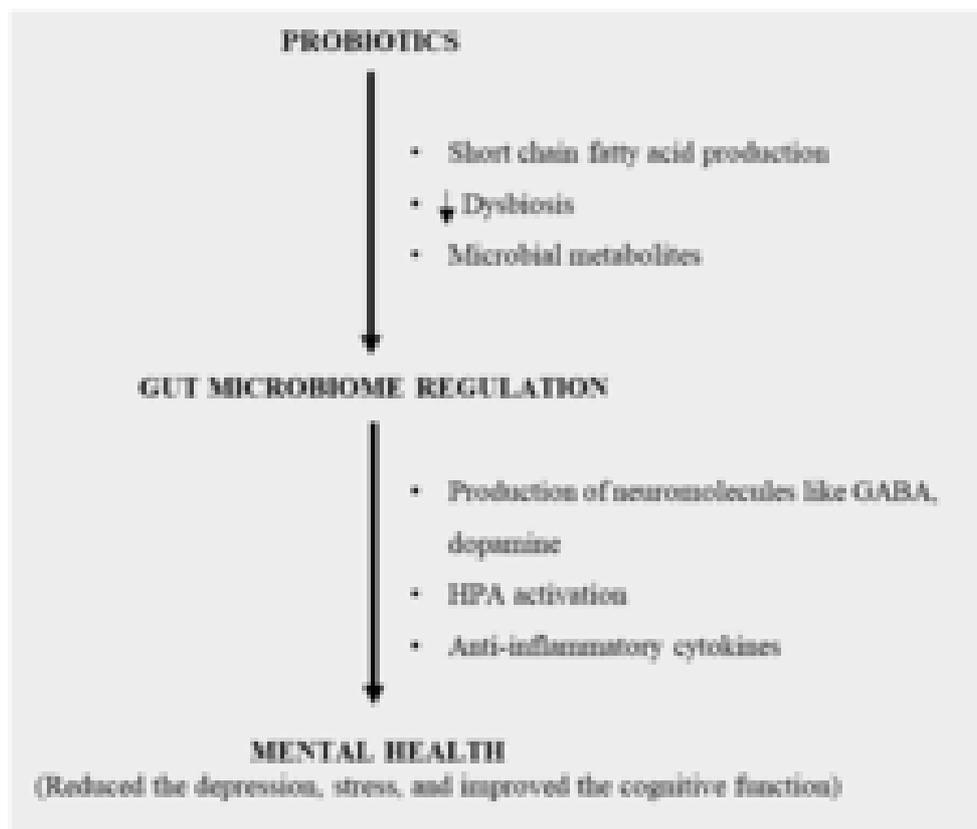


Figure 1: Effect of probiotic on mental health status via gut microbial regulation

DECLARATIONS

Acknowledgement

The authors thankfully acknowledge Chiang Mai University (CMU) for a grant and the Faculty of Pharmacy, Chiang Mai University for support. BSS and PK gratefully acknowledge CMU for Post-Doctoral Fellowship. MIP wishes to thank Ratchadaphiseksomphot Endowment Fund for Postdoctoral Fellowship, Chulalongkorn University, Thailand, for the support.

Conflict of interest

The authors declare that there is no conflict of interest with regards to this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. BSS, MIP, and PK contributed to the conception and design, acquisition, manuscript preparation, and critical revision of the manuscript. All the authors contributed significantly and they all agree with the content of the manuscript.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. Chutkan R. *The microbiome solution: A radical new way to heal your body from the inside out*. 1st edn, New York: Avery; 2015; p 298.
2. Choi J, Hur T-Y, Hong Y. Influence of altered gut microbiota composition on aging and aging-related diseases. *J Lifestyle Med* 2018; 8(1): 1-7.
3. Sivamaruthi BS, Kesika P, Chaiyasut C. Influence of probiotic supplementation on climacteric symptoms in menopausal women - A mini review. *Int J App Pharm* 2018; 10(6): 43-46.
4. Sivamaruthi BS, Kesika P, Chaiyasut C. A review on anti-aging properties of probiotics. *Int J App Pharm* 2018; 10(5): 23-27.

5. Sivamaruthi BS, Kesika P, Chaiyasut C. Probiotic based therapy for atopic dermatitis: outcomes of clinical studies - A mini review. *Asian Pac J Trop Biomed* 2018; 8(6): 328-332.
6. Sivamaruthi BS. A comprehensive review on clinical outcome of probiotic and synbiotic therapy for inflammatory bowel diseases. *Asian Pac J Trop Biomed* 2018; 8(3): 179-186.
7. Skórka A, Pieścik-Lech M, Kołodziej M, Szajewska H. To add or not to add probiotics to infant formulae? An updated systematic review. *Benef Microbes* 2017; 8(5): 717-725.
8. Vandenplas Y, Zakharova I, Dmitrieva Y. Oligosaccharides in infant formula: more evidence to validate the role of prebiotics. *Br J Nutr* 2015; 113(9): 1339-1344.
9. Miranda VH, Cássio R, Correia-Guedes L, Gomes MA, Chegao A, Miranda E, Soares T, Coelho M, Rosa MM, Ferreira JJ, et al. Posttranslational modifications of blood-derived alpha-synuclein as biochemical markers for Parkinson's disease. *Sci Rep* 2017; 7: 13713. DOI: 10.1038/s41598-017-14175-5.
10. Mason BL. Feeding systems and the gut microbiome: Gut-brain interactions with relevance to psychiatric conditions. *Psychosomatics* 2017; 58(6): 574-580.
11. Dinan TG, Cryan JF. Brain-gut-microbiota axis and mental health. *Psychosom Med* 2017; 79(8): 920-926.
12. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The gut microbiome and mental health: Implications for anxiety- and trauma-related disorders. *OMICS* 2018; 22(2): 90-107.
13. Gupta V, Nag D, Garg P. Recurrent urinary tract infections in women: How promising is the use of probiotics?. *Indian J Med Microbiol* 2017; 35(3): 347-354.
14. Xu W, Judge MP, Maas K, Hussain N, McGrath JM, Henderson WA, Cong X. Systematic review of the effect of enteral feeding on gut microbiota in preterm infants. *J Obstet Gynecol Neonatal Nurs* 2018; 47(3): 451-463.
15. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: An integrative view. *Cell* 2012; 148(6): 1258-1270.
16. Zivkovic AM, German JB, Lebrilla CB, Mills DA. Human milk glycometabolome and its impact on the infant gastrointestinal microbiota. *Proc Natl Acad Sci U S A* 2011; 108(Suppl 1): 4653-4658.
17. Marcobal A, Barboza M, Froehlich JW, Block DE, German JB, Lebrilla CB, Mills DA. Consumption of human milk oligosaccharides by gut-related microbes. *J Agric Food Chem* 2010; 58(9): 5334-5340.
18. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. *Front Neurosci* 2015; 9: 194. DOI: 10.3389/fnins.2015.00194.
19. Bruce-Keller AJ, Fernandez-Kim SO, Townsend RL, Kruger C, Carmouche R, Newman S, Salbaum JM, Berthoud HR. Maternal obese-type gut microbiota differentially impact cognition, anxiety and compulsive behavior in male and female offspring in mice. *PLoS One* 2017; 12(4): e0175577. DOI: 10.1371/journal.pone.0175577.
20. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for prevention of atopy and food hypersensitivity in early childhood: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016; 95(8): e2562. DOI: 10.1097/MD.0000000000002562.
21. Collen A. *10% Human: How Your Body's Microbes Hold the Key to Health and Happiness*. 1st ed. New York: HarperCollins Publishers; 2015. 336 p.
22. Logan AC, Jacka FN, Craig JM, Prescott SL. The microbiome and mental health: looking back, moving forward with lessons from allergic diseases. *Clin Psychopharmacol Neurosci* 2016; 14(2): 131-147.
23. Gershon MD, Tack J. The serotonin signaling system: From basic understanding to drug development for functional GI disorders. *Gastroenterology* 2007; 132(1): 397-414.
24. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015; 161(2): 264-276.
25. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, Korecka A, Bakocevic N, Ng LG, Kundu P, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med* 2014; 6(263): 263ra158. DOI:10.1126/scitranslmed.3009759.
26. Liang S, Wu X, Hu X, Wang T, Jin F. Recognizing depression from the microbiota-gut-brain axis. *Int J Mol Sci* 2018; 19(6): 1592. DOI: 10.3390/ijms19061592.
27. Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, Macqueen G, Sherman PM. Bacterial infection causes stress-induced memory dysfunction in mice. *Gut* 2011; 60(3): 307-317.
28. Jiao S-S, Shen L-L, Zhu C, Bu X-L, Liu Y-H, Liu C-H, Yao X-Q, Zhang L-L, Zhou H-D, Walker DG, et al. Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. *Transl Psychiatry* 2016; 6: e907. DOI: 10.1038/tp.2016.186.
29. Verdino J. The third tier in treatment: Attending to the growing connection between gut health and emotional well-being. *Health Psychol Open* 2017; 4(2): 2055102917724335. DOI: 10.1177/2055102917724335.
30. Cerdó T, Ruíz A, Suárez A, Campoy C. Probiotic, prebiotic, and brain development. *Nutrients* 2017; 9: 1247. DOI:10.3390/nu9111247.
31. Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. In: Lyte, Mark, Cryan, John, editors. *Microbial endocrinology: The microbiota-gut-brain axis in health and disease*. Advances in Experimental Medicine and Biology. 1st ed. New York: Springer; 2014. Vol 817. p 195-219.
32. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* 2016; 165(7): 1762-1775.

33. O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, Cryan JF, Dinan TG. Early life stress alters behavior, immunity, and microbiota in rats: Implications for irritable bowel syndrome and psychiatric illnesses. *Biol Psychiatry* 2009; 65(3): 263-267.
34. Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, Deng Y, Blennerhassett P, Macri J, McCoy KD, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology* 2011; 141(2): 599-609.
35. Messaoudi M, Violle N, Bisson JF, Desor D, Javelot H, Rougeot C. Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers. *Gut Microbes* 2011; 2(4): 256-261.
36. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr* 2007; 61(3): 355-361.
37. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behav Immun* 2015; 48: 258-264.
38. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Memarzadeh MR, Asemi Z, Esmailzadeh A. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition* 2016; 32(3): 315-320.
39. Jadrešin O, Hojsak I, Mišak Z, Kekez AJ, Trbojević T, Ivković L, Kolaček S. *Lactobacillus reuteri* DSM 17938 in the treatment of functional abdominal pain in children: RCT Study. *J Pediatr Gastroenterol Nutr* 2017; 64(6): 925-929.
40. Kałużna-Czaplińska J, Błaszczuk S. The level of arabinitol in autistic children after probiotic therapy. *Nutrition* 2012; 28(2): 124-126.
41. West R, Roberts E, Sichel LS, Sichel J. Improvements in gastrointestinal symptoms among children with autism spectrum disorder receiving the delpro® probiotic and immunomodulator formulation. *J Prob Health* 2013; 1(1): 102. DOI: 10.4172/jph.1000102.
42. Jasarevic E, Howerton CL, Howard CD, Bale TL. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. *Endocrinology* 2015; 156(9): 3265-3276.
43. Marcos A, Wärnberg J, Nova E, Gómez S, Alvarez A, Alvarez R, Mateos JA, Cobo JM. The effect of milk fermented by yogurt cultures plus *Lactobacillus casei* DN-114001 on the immune response of subjects under academic examination stress. *Eur J Nutr* 2004; 43(6): 381-389.
44. Romijn AR, Rucklidge JJ, Kuijter RG, Frampton C. A double-blind, randomized, placebo-controlled trial of *Lactobacillus helveticus* and *Bifidobacterium longum* for the symptoms of depression. *Aust N Z J Psychiatry* 2017; 51(8): 810-821.
45. Chung Y-C, Jin H-M, Cui Y, Kim DS, Jung JM, Park JI, Jung E-S, Choi E-K, Chae S-W. Fermented milk of *Lactobacillus helveticus* IDCC3801 improves cognitive functioning during cognitive fatigue tests in healthy older adults. *J Funct Foods* 2014; 10: 465-474.
46. Saarela MH. Safety aspects of next generation probiotics. *Curr Opin Food Sci* 2019; 30: 8-13.
47. Neef A, Sanz Y. Future for probiotic science in functional food and dietary supplement development. *Curr Opin Clin Nutr Metab Care* 2013; 16(6): 679-687.
48. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science* 2011; 332(6032): 974-977.
49. Udayappan S, Manneras-Holm L, Chaplin-Scott A, Belzer C, Herrema H, Dallinga-Thie GM, Duncan SH, Stroes ESG, Groen AK, Flint HJ, et al. Oral treatment with *Eubacterium hallii* improves insulin sensitivity in db/db mice. *NPJ Biofilms Microbiomes* 2016; 2: 16009. DOI: 10.1038/npjbiofilms.2016.9.
50. El Hage R, Hernandez-Sanabria E, Van de Wiele T. Emerging trends in "Smart Probiotics": Functional consideration for the development of novel health and industrial applications. *Front Microbiol* 2017; 8: 1889. DOI: 10.3389/fmicb.2017.01889.