Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/29/20240754

Potential therapeutic targets in the gut-brain axis for depression

Yixin Xu

College of William and Mary

monicayixn@gmail.com

Abstract. As an essential counterpart of the human internal environment, the gut microbiome has been investigated extensively in light of multiple diseases. This study aims to find out potential treatments for depression by altering gut microbiome composition in order to alleviate side effects caused by traditional medications. According to previous findings, the human gut correlates with the brain through pathways known as the gut-brain axis. Two genera of microbiome, Lactobacillus and Bifidobacterium, have been mentioned by researchers to be crucial to depression-related neurotransmitter secretion in GBA. Besides, they have already been used in clinical as effective probiotics for gut-related diseases. The paper hypothesized particular interactions between the two genera and the human nerve that enable them to be therapeutic cures in adequate amounts. In this study, a range of available single-cell data about "depression" and "lactobacillus and bifidobacterium" were analyzed and adjusted into proper figures. I discuss the efficacy of different species, concentrations, and other elements of those probiotics, eventually proposing a novel way of treating and classifying depressive disorders. The study puts forth a perspective of maintaining a depression-free state with an internal factor, the gut microbiome, instead of targeting the efferent neurons directly with external drugs which could cause resistance and severe side effects.

Keywords: Microbiome, Depression, Lactobacillus, Bifidobacterium, probiotics, Gut-Brain Axis

1. Introduction

Depression is a prevalent mental disorder globally and contributes significantly to the overall global disease burden [1]. The disease used to be pervasive among working-aged people, yet it has also become a growing problem in children, adolescents, and elders recently [1]. In general, depression is characterized by persistent hopelessness, loss of interest, fatigue, appetite change, etc. The symptoms could interrupt patients' social activities and even lead to detrimental effects on their physical well-being (DMS V). The pandemic adversely affected the incidence of depression [2]. Before COVID-19, 24.7% (95% CI, 22.9% -26.6%) of US citizens experienced depression, but this number rose to 52.5% (95% CI, 49.1% -55.8%, Fig 1A). Among this population, the prevalence of mild depression symptoms increased from 16.2% to 24.6%; moderate ones rose from 5.7% to 14.8%; severe depression reached 7.9% from 2.1% (Fig 1B). The quantity of prescribed antidepressant items rose from 61.9 million in 2015/2016 to 83.5 million in 2021/2022, marking a 34.8% increase (Fig 1C).

Given the soaring clinical and social impact of depression, scientists put forth much attention on it.

DOI: 10.54254/2753-8818/29/20240754

While the entire etiopathology remains unclear, researchers in the field commonly recognize monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine, as the largest contributors [3]. Consequently, serotonin-selective reuptake inhibitors (SSRIs) medications are widely used as the first-line treatment [4]. However, approximately 40% of patients who were prescribed SSRIs reported to experience side effects (Fig 1D). Patients often report symptoms such as sexual dysfunction, weight fluctuations, headaches, insomnia, and emotional numbness [5]. In addition, most patients also develop tolerance to SSRIs after specific doses of the drug. Thus, there is an urgent need to foster therapeutics with few adverse symptoms and less organic damage.

That is when the gut microbiome comes into view. As the combination of microorganisms colonizes the human gastrointestinal (GI) tract, gut microbiota takes the role of keeping homeostasis of the gut as well as the body parts that are related to the gut. According to current research, the gut and the central nervous system (CNS), where various neurotransmitter receptors are located, are correlated, and multiple interactions occur via the pathways [6]. Such bidirectional signaling pathways are referred to as the gut-brain axis (GBA) [6]. More evidence is proving that gut microbes may alter the activities of the CNS and neurotransmitters through GBA, therefore curing depressive disorders [7]. Furthermore, rebalancing the microbial community reduces the risk of causing dysfunction in other systems. In 2007, the Human Microbiome Project (HMP) primarily used whole metagenome shotgun (mWGS) sequencing and 16S metagenomic sequencing to build up a data collection of microorganisms living within the human body. According to HMP, the human GI tract holds approximately 1000 species of microbes and no less than 1E4 microorganisms [8]. The reduction of general microbial diversity within the gut could also relate, though not necessarily causal, to depressive symptoms [9].

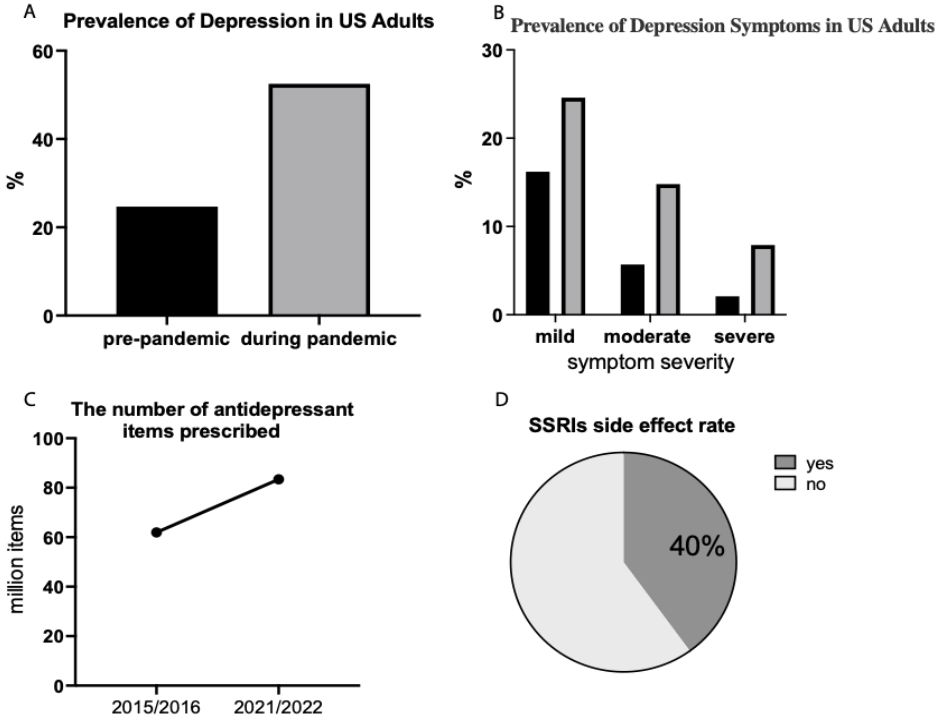

Figure 1. Depression trends and treatment in the USA before and during the pandemic. A. Prevalence of depression in US adults. B. Prevalence of depression symptoms in US adults. C. The number of antidepressant items prescribed. D. SSRIs side effect rate. Adapted based on Ettman et al., 2020 [2] & Burns, 2022 [10].

2. Rational

The Microbiota-Gut-Brain (MGB) axis enables two-way communication between the gut and brain through neural, endocrine, and immune channels, incorporating the microbiota and their byproducts. In

DOI: 10.54254/2753-8818/29/20240754

Major Depressive Disorder (MDD), shifts in microbial populations disturb the gut's equilibrium, causing digestive problems, inflammation, and "leaky gut" conditions. The gut's Enteric Nervous System (ENS) and the vagus nerve help convey these microbial signals to the brain. These messages can lead to brain inflammation, instigating changes in neural pathways and the release of cortisol, which further affects gut health and can intensify depression. Other signaling and metabolic systems, like the endocannabinoid mechanism, CAMKII-CREB and MAPK pathways, glycerophospholipid metabolism, and mitochondrial functions, are also involved. This intricate web of interactions makes studying the role of gut microbiota in depression challenging, as illustrated in Fig 2.

The relationship between the gut microbiome and the host's nervous system affects depression through various mechanisms. More than ten genera of gut microbiota species are proven to have an association with depressive symptoms. For example, Sellimonas, Lachnoclostridium, Hungatella, Ruminococcus, Subdoligranulum, LachnospiraceaeUCG001, Eubacterium ventriosum and Ruminococcusgauvreauii group are involved in GABA and serotonin synthesis. Among the gut microbiome, lactobacillus and bifidobacteria species are indirectly influencing depression [9]. Since the two genera have been extensively researched and used as probiotics in other diseases, this paper will discuss their potential in treating and classifying depressive disorders and introduce hypotheses of their interactions with the host nervous system as well as each other [11]. The paper also refers to HMP and other databases to create statistical models that support the hypotheses.

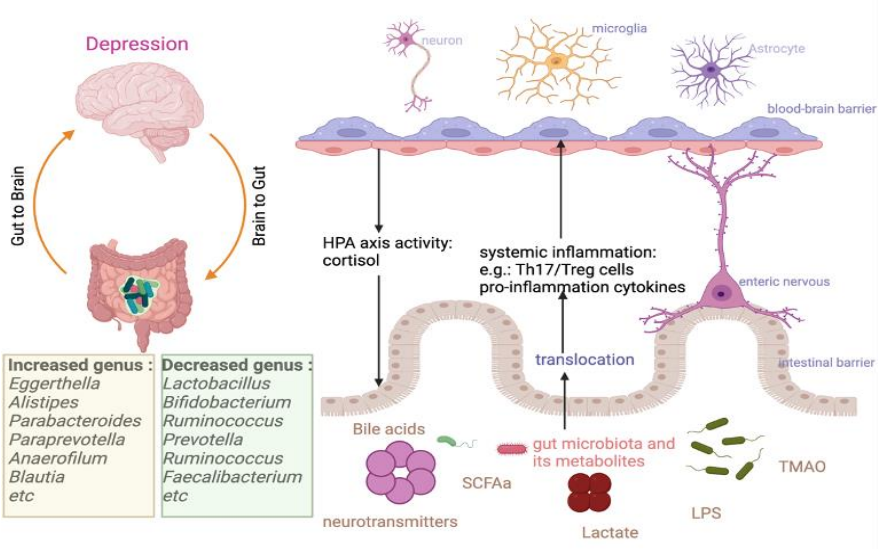

Figure 1. Interventions aimed at the microbiota to address depression and their effects on the gut-brain axis. HPA, hypothalamic - pituitary - adrenal; LPS, lipopolysaccharide; TMAO, Trimethylamine-N-oxide. Adapted based on Liu et al., 2023 [12] & Liu et al., 2022 [13].

As neurotransmitters directly related to depression, the bacteria could modulate depression level [14]. This study focuses on the two genera, Lactobacillus and Bifidobacterium, that have been shown to have the closest relationships with the host CNS (Fig 3). These lactic acid bacteria (LAB) are abundant in human gut microbiota composition, and due to their specific properties, like gram-positive and easy cultivation, they have been used pervasively as effective probiotics for gut dysfunctions [15].

3. Results

In response to the pressing need for improved depression treatments, an increasing number of scientists are focusing on exploring alternative approaches through the study of the gut microbiome's connection to depression (Figure 3). In 2022, there were 349 papers investigating this relationship, a significant increase from 134 papers in 2018 (PubMed.com search (Figure 3A). Evidence strongly suggests that individuals with MDD have a distinct gut microbiome compared to healthy individuals (See Figure 3C,

DOI: 10.54254/2753-8818/29/20240754

[16]). Among the promising candidate gut microbiome, Lactobacillus (17.8% in 2020 and 20.1% in 2022) and Bifidobacterium (10.3% in 2020 and 16.9% in 2022) have garnered the most attention (Figure 3B). In general, treatment with Lactobacillus and Bifidobacterium can reverse the alternation in hypothalamic-pituitary-adrenal (HPA) axis modulation which is correlated to mood disorders [7]. Lactibacillus farciminis, to be specific, activates the HPA axis and reverses leaky gut caused by chronic stress, therefore enabling the regular processes of the GBA. L. rhamnosus (JB-1) is effective in alleviating depressive symptoms by changing neurotransmitter behaviors: JB-1 administration reduces stress-related corticosterone levels, increases GABAB1b receptors in the prefrontal cortex, and reduces GABAA α 2 receptors in the amygdala of animal models. Since the decline in prefrontal cortex-GABA receptor level and elevation in the amygdala-GABA receptor level is prevalent among depressed animals, JB-1 ought to be a promising strain in this study [7]. It is not surprised to see that MDD patients have significantly reduced amount of Bifidobacterium and moderate reduction in Lactobacillus (Figure 3D, [17]). Furthermore, L. reuteri could inhibit the translocation of transcription factor NF- κ B toward the nuclei of intestinal epithelial cells (IEC), thus stimulating the production of nerve growth factor [18]. The blend of L. acidophilus and Bifidobacterium animalis subsp. lactis modifies the TLR2-mediated NF- κ B signaling route in inflamed IECs [11]. B. infantis can reverse the increase in stress susceptibility in murine models by stabilizing hormonal responses [19]. Another species, B. adolescentis, is effective in converting precursor to GABA, alleviating depressive symptoms [20].

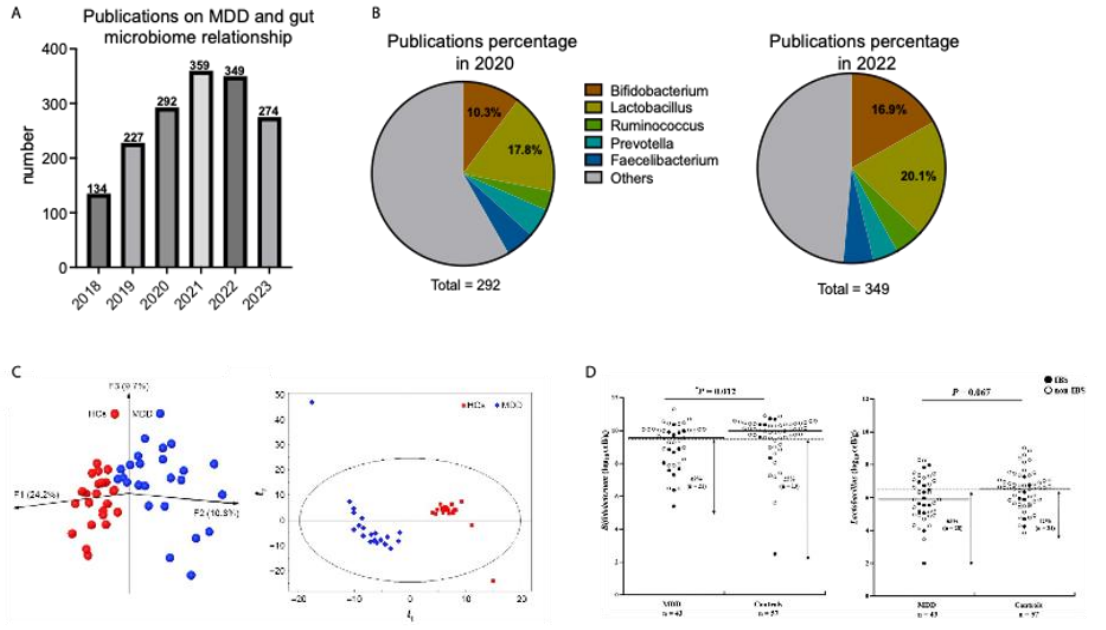

Figure 2. Comparison of bacterial counts in the gut microbiota between patients (MDD) and controls. A. The total publications exploring the MDD-gut microbiome relationship on PubMed between 2018 and 2023. B. Differing percentages of publications examining the link between various types of gut microbiome and depression. C. Clear distinctions in gut microbial composition between MDD and healthy controls (HC). D. Left, Bifidobacterium counts. Right, Lactobacillus counts. Dotted lines represent optimal cut-off point estimated by ROC analysis. MDD: major depressive disorder. C &D credits to Figure 1 in Emiko et al., 2016 [17] and Figure 1 in Chen et al., 2018 [16].

Despite individual effects, these probiotics tend to interact with each other at the molecular level, producing molecules essential for mood disorders. Bacteria interact with each other through a special process called quorum sensing (QS), in which gram-positive bacteria like Lactobacillus and Bifidobacterium secret oligopeptide. Some of these peptides could either pass the Blood-Brain Barrier (BBB), the defense mechanism within the human brain that could filter unpleasant molecules out of the

DOI: 10.54254/2753-8818/29/20240754

CNS or affect its permeability [19]. Nevertheless, the interaction between peptide and host depression-related functions like neurotransmitter production is still yet to be identified. In other words, researchers have proved QS peptides could somehow alter brain function while the detailed mechanisms related to depression need further investigation. Despite QS, Lactobacillus and Bifidobacterium are positively correlated, meaning that the combined use of these probiotics enhances the function of both genera [20].

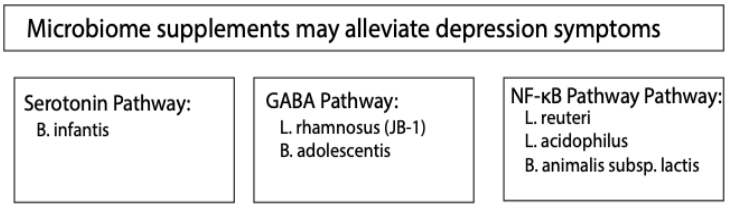

Figure 3. Potential Probiotic Pathways in Alleviating Depression Symptoms. Serotonin Pathway: Highlights the role of "B. infantis" in influencing the serotonin pathway, which is essential for mood regulation. GABA Pathway: Emphasizes the importance of "L. rhamnosus (JB-1)" and "B. adolescentis" in the GABA neurotransmission pathway, crucial for mood and anxiety regulation. NF-κB Pathway: Lists "L. reuteri," "L. acidophilus," and "B. animalis subsp. lactis" as influential agents in the NF-κB pathway, which is associated with inflammation and mood regulation.

4. Conclusion

Scientific findings underscore the complex interplay between gut microbiome alterations and depression types, offering insights into potential categorization based on microbial dysregulation. Given the limited responsiveness of many patients to current treatments, it is now imperative to reconsider how we categorize types of depression based on the specific microbiome dysfunctions involved (Figure 4). This article offers an in-depth exploration of how the gut microbiome and neurotransmitters interact and potentially impact depression. It potentially serves as a valuable resource for guiding the re-categorization of depression types.

Lactobacillus rhamnosus (JB-1) intake showed a decrease in stress-triggered corticosterone levels, indicating a notable effect on the CNS [7]. Given that elevated GABAA α 2 mRNA levels in the amygdala are characteristic of stressed animals, these findings suggest that Lactobacillus could provide an adaptive advantage in coping with stressful situations [7]. Bifidobacteria's ability to inhibit NF- κ B activation in intestinal epithelial cells (IECs) is strain-dependent [11]. For instance, B. bifidum shows promise in mitigating inflammatory gastrointestinal diseases. Notably, these probiotics interact through quorum sensing, influencing the Blood-Brain Barrier. Their precise effects on depression require further study, but the potential is encouraging. Combining Lactobacillus and Bifidobacterium enhances their function, suggesting a synergistic depression treatment approach.

Given the considerable side effects and limited effectiveness of SSRIs in some cases, the quest for alternative therapeutics is of paramount importance. Towards this goal, being able to better classify depression based on microbiome may be the key first step. The use of specific probiotics to influence the gut-brain axis could represent a novel approach to treating depression. By targeting specific pathways related to depression, it's possible that we could see better-tailored treatments. Incorporating these findings into a broader treatment plan requires careful consideration. While these probiotics may offer a potential adjunctive treatment, they shouldn't replace current evidence-based treatments for depression without further research. Among many microbiota candidates, promising targets for treating depression lie in enhancing the roles of Lactobacillus and Bifidobacterium. These probiotics have shown potential in restoring gut-brain axis balance, modulating neurotransmitters, and countering stress-related issues, offering a potentially safer and more effective avenue for depression treatment.

DOI: 10.54254/2753-8818/29/20240754

Acknowledgment

I would like to acknowledge the people who contributed to the successful completion of my work. First of all, I would like to thank my mentor Ms. Yandan Wang, who pointed out the direction of the project, tutored me with the data analysis methods, and availed me with the production of the figures. Secondly, I would like to thank my parents, who have shown great tolerance to me, unreservedly supported my bold ideas, and encouraged me to move a step further. This study is based on my previous exploration of depression and gut microbiota, aiming to give feasible solutions. Due to limited lab recourses, the project was conducted with the existing database.

References

[1] Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, J. L., Vos, T., & Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLoS Medicine, 10(11). https://doi.org/10.1371/journal.pmed.1001547

[2] Abeysekera, N. W. B. Y., & De Zoysa, E. (2021). Higher prevalence of geriatric depression, catastrophizing pain and sleep disorders in institutionalized elders: a cross-sectional study in Galle District, Sri Lanka. BMC geriatrics, 21(1), 685. https://doi.org/10.1186/s12877-021-02536-9

[3] Shorey, S., Ng, E. D., & Wong, C. H. J. (2022). Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis. The British journal of clinical psychology, 61(2), 287–305. https://doi.org/10.1111/bjc.12333

[4] Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(9):e2019686. doi:10.1001/jamanetworkopen.2020.19686

[5] Hirschfeld R. M. (2000). History and evolution of the monoamine hypothesis of depression. The Journal of clinical psychiatry, 61 Suppl 6, 4 – 6. https://www.psychiatrist.com/jcp/depression/history-evolution-monoamine-hypothesis-depression/

[6] Micheli, L., Ceccarelli, M., D'Andrea, G., & Tirone, F. (2018). Depression and adult neurogenesis: Positive effects of the antidepressant fluoxetine and of physical exercise. Brain research bulletin, 143, 181–193. https://doi.org/10.1016/j.brainresbull.2018.09.002

[7] Demyttenaere, K., & Jaspers, L. (2008). Review: Bupropion and SSRI-induced side effects. Journal of psychopharmacology (Oxford, England), 22(7), 792 – 804. https://doi.org/10.1177/0269881107083798

[8] Murrough, J. W., Yaqubi, S., Sayed, S., & Charney, D. S. (2015). Emerging drugs for the treatment of anxiety. Expert opinion on emerging drugs, 20(3), 393–406.

[9] Altaf, R., Gonzalez, I., Rubino, K., & Nemec, E. C., 2nd (2021). Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: Systematic review & meta-analysis. Complementary therapies in medicine, 61, 102770.

[10] Rhee, S. H., Pothoulakis, C., & Mayer, E. A. (2009). Principles and clinical implications of the brain-gut-enteric microbiota axis. Nature reviews. Gastroenterology & hepatology, 6(5), 306–314. https://doi.org/10.1038/nrgastro.2009.35

[11] Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & 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 of the United States of America, 108(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

[12] Fujimura, K. E., Slusher, N. A., Cabana, M. D., & Lynch, S. V. (2010). Role of the gut microbiota in defining human health. Expert review of anti-infective therapy, 8(4), 435 – 454. https://doi.org/10.1586/eri.10.14

[13] Kelly, J. R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., Kennedy, P. J., Beers, S., Scott, K., Moloney, G., Hoban, A. E., Scott, L., Fitzgerald, P., Ross, P., Stanton, C., Clarke, G., Cryan, J. F., & Dinan, T. G. (2016). Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. Journal of Psychiatric Research, 82, 109-118. https://doi.org/10.1016/j.jpsychires.2016.07.019

[14] Burns, C. (2022). Antidepressant prescribing increases by 35% in six years. The Pharmaceutical Journal, PJ, Vol 309, 7963;309(7963). doi:10.1211/PJ.2022.1.149158

[15] Li, S. C., Hsu, W. F., Chang, J. S., & Shih, C. K. (2019). Combination of Lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis Shows a Stronger Anti-Inflammatory Effect than Individual Strains in HT-29 Cells. Nutrients, 11(5), 969. https://doi.org/10.3390/nu11050969

[16] Liu, L., Wang, H., Chen, X., Zhang, Y., Zhang, H., & Xie, P. (2023). Gut microbiota and its metabolites in depression: from pathogenesis to treatment. EBioMedicine, 90, 104527. https://doi.org/10.1016/j.ebiom.2023.104527

[17] Liu, L., Wang, H., Zhang, H., Chen, X., Zhang, Y., Wu, J., Zhao, L., Wang, D., Pu, J., Ji, P., & Xie, P. (2022). Toward a Deeper Understanding of Gut Microbiome in Depression: The Promise of Clinical Applicability. Advanced science (Weinheim, Baden-Wurttemberg,Germany), 9(35), e2203707. https://doi.org/10.1002/advs.202203707

[18] Radjabzadeh, D., Bosch, J. A., Uitterlinden, A. G., Zwinderman, A. H., Ikram, M. A., Van Meurs, J. B., Luik, A. I., Nieuwdorp, M., Lok, A., Van Duijn, C. M., Kraaij, R., & Amin, N. (2022). Gut microbiome-wide association study of depressive symptoms. Nature Communications, 13(1), 1-10. https://doi.org/10.1038/s41467-022-34502-3

[19] O'Callaghan, J., & O'Toole, P. W. (2013). Lactobacillus: host-microbe relationships. Current topics in microbiology and immunology, 358, 119–154. https://doi.org/10.1007/82_2011_187

[20] Chen, J. J., Zheng, P., Liu, Y. Y., Zhong, X. G., Wang, H. Y., Guo, Y. J., & Xie, P. (2018). Sex differences in gut microbiota in patients with major depressive disorder. Neuropsychiatric disease and treatment, 14, 647–655. https://doi.org/10.2147/NDT.S159322

[21] Emiko Aizawa, Hirokazu Tsuji, Takashi Asahara, Takuya Takahashi, Toshiya Teraishi, Sumiko Yoshida, Miho Ota, Norie Koga, Kotaro Hattori, Hiroshi Kunugi. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder, Journal of Affective Disorders, Volume 202, 2016, Pages 254-257, ISSN 0165-0327,https://doi.org/10.1016/j.jad.2016.05.038.

[22] Marco, M. L., Pavan, S., & Kleerebezem, M. (2006). Towards understanding molecular modes of probiotic action. Current opinion in biotechnology, 17(2), 204 – 210. https://doi.org/10.1016/j.copbio.2006.02.005

[23] Wynendaele, E., Verbeke, F., Stalmans, S., Gevaert, B., Janssens, Y., Van De Wiele, C., et.al. (2015). Quorum Sensing Peptides Selectively Penetrate the Blood-Brain Barrier. PloS one, 10 (11), e0142071.

[24] Medina-Rodriguez, E. M., Madorma, D., O'Connor, G., Mason, B. L., Han, D., Deo, S. K., et.al. (2020). Identification of a Signaling Mechanism by Which the Microbiome Regulates Th17 Cell-Mediated Depressive-Like Behaviors in Mice. The American journal of psychiatry, 177 (10), 974–990.

[25] Duranti, S., Ruiz, L., Lugli, G. A., Tames, H., Milani, C., Mancabelli, L., Mancino, W., Longhi, G., Carnevali, L., Sgoifo, A., Margolles, A., Ventura, M., Ruas-Madiedo, P., & Turroni, F. (2020). Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Scientific reports, 10(1), 14112. https://doi.org/10.1038/s41598-020-70986-z

[26] Luo, J., Li, Y., Xie, J., Gao, L., Liu, L., Ou, S., Chen, L., & Peng, X. (2018). The primary biological network of Bifidobacterium in the gut. FEMS Microbiology Letters, 365(8). https://doi.org/10.1093/femsle/fny057