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Issue **Article**

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PSYCHOBIOTIC POTENTIAL OF LACTOBACILLUS STRAINS IN ASD BEHAVIORAL MODULATION

Abstract: *Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication, repetitive behaviors, and heightened sensitivity to stress. In recent years, increasing evidence has highlighted the significance of the gut–brain axis, which reflects the functional interaction between the gut microbiota and the central nervous system, in the pathophysiology of ASD. This article examines the psychobiotic potential of Lactobacillus strains in modulating ASD-associated behavioral disturbances.*

The study discusses the modulation of gut–brain axis signaling, the effects on hypothalamic–pituitary–adrenal (HPA) axis activity, reductions in cortisol levels, and attenuation of stress reactivity. In addition, the influence of Lactobacillus strains on the expression of brain-derived neurotrophic factor (BDNF), as well as their capacity to synthesize γ-aminobutyric acid (GABA), short-chain fatty acids (SCFAs), and metabolites involved in dopamine signaling, is analyzed. Furthermore, the effects of Lactobacillus strains on the serotonergic system via tryptophan metabolism and their immunomodulatory properties are highlighted. The findings indicate that Lactobacillus strains represent a promising psychobiotic approach as an adjunctive strategy for ASD management.

Key words: *Gut–brain axis, Vagus nerve, HPA axis, CNS, Blood–brain barrier, Hippocampus, Gut microbiota, Lactobacilli strains, Probiotics, Psychobiotics, Neurotransmitters, GABA, Serotonin, Dopamine, Cortisol, BDNF, Tryptophan, SCFAs, Neuroinflammation, Cytokines, Immunomodulation, Stress resilience, ASD, Vagotomy.*

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Introduction

Modulation of the gut–brain axis signaling

The regulation of vagus-dependent neurosignaling by Lactobacilli strains is a complex process involving multiple pathways and mechanisms that influence brain function and behavior. Several studies highlight the pivotal role of the vagus nerve as a communication conduit between the gut microbiota and the central nervous system (CNS). For instance, ingestion of Lactobacillus strains has been shown to modulate emotional behavior through vagus nerve-mediated pathways. Specifically, a study demonstrated that Lactobacillus rhamnosus (JB-1) administration resulted in region-specific alterations in GABA B1b mRNA expression in the brain, an effect dependent on vagal signaling [Liu Q., 2023.]. Further evidence supports the notion that Lactobacillus strains can influence neurochemical pathways via vagus-dependent mechanisms. The same strain, L. rhamnosus JB-1, was shown to decrease certain gut-derived proteins in a manner reliant on vagal pathways, underscoring the importance of the vagus nerve in microbiota-brain communication [Bostick J. W., 2024.]. Additionally, the modulation of emotional and behavioral responses by Lactobacillus strains appears to involve the vagus nerve's anti-inflammatory pathways, which are linked to parasympathetic nervous system activity and stress regulation [Tracey K. J. 2023.]. Interventions targeting vagal signaling, such as vagotomy, have been observed to alter the beneficial effects of probiotics, indicating that vagus-dependent neurosignaling is crucial for probiotic efficacy. For example, the therapeutic benefits of probiotics, including Lactobacillus strains, are strain-dependent and often rely on intact vagal pathways to exert their effects on the brain [Cryan J. F., 2024]. Moreover, oral administration of Lactobacillus strains has been associated with changes in avoidance behavior and social deficits, further emphasizing the role of vagus-dependent signaling in behavioral modulation [Luk B., 2022.].The influence of Lactobacilli on neurodevelopment and neuroinflammation also appears to involve vagal pathways. In preterm infants, gut microbiota, including Lactobacillus strains, interact with the vagus nerve and hypothalamic–pituitary–adrenal axis to impact neurodevelopmental outcomes [Luk B., 2022.]. Similarly, the regulation of hippocampal plasticity, inflammation, and behaviors related to hippocampal function has been linked to gut microbiota, with Lactobacillus strains playing a significant role through vagus-dependent mechanisms [Caspani G., 2022.]. Finally, the potential therapeutic implications of modulating vagus-dependent neurosignaling are underscored by research into neuroimmune interactions. The parasympathetic nervous system, via vagal anti-inflammatory pathways, modulates stress responses and may be harnessed to treat neurological disorders. Probiotics, including Lactobacillus strains, are being investigated for their capacity to influence these pathways, with evidence suggesting that their benefits are mediated through vagus nerve-dependent signaling [Cryan J. F., 2020. Tracey K. J. 2023. Farsani A. M., 2023]. In summary, the existing literature underscores the centrality of the vagus nerve in mediating the neurosignaling effects of Lactobacilli strains. These effects encompass modulation of neurochemical pathways, behavioral responses, neuroinflammation, and neurodevelopment, highlighting the potential of targeting vagus-dependent pathways for therapeutic interventions involving gut microbiota [Bravo J. A., 2011. Liu Q., 2023. Bravo J. A., 2011. Bostick J. W., 2024. Cryan J. F., 2020. Tracey K. J. 2023. Luk B., 2022. Dahl C., 2021. Caspani G., 2022. Farsani A. M., 2023.].

Modulatory effects on the hypothalamic–pituitary–adrenal (HPA) axis

The modulation of the hypothalamic-pituitary-adrenal (HPA) axis by probiotic strains, particularly lactobacilli, has garnered increasing scientific interest due to its implications for stress regulation and neuroendocrine function. Several studies highlight the capacity of specific Lactobacillus strains to influence HPA axis activity, thereby affecting stress responses and related physiological processes. Research indicates that certain Lactobacillus strains can modulate HPA axis activity, which is central to the body's stress response. For instance, strains of Lactobacillus have been shown to lower HPA axis activation, leading to reduced stress-induced hormonal responses [Sharma R., 2021.]. Similarly, ingestion of Lactobacillus strains has been associated with regulation of emotional behavior, suggesting a direct link between gut microbiota modulation and HPA axis activity [Bravo J. A., 2011.]. The ability of these probiotics to influence stress responses is further supported by findings that they can modulate cytokine levels, which are known to interact with the HPA axis [Wang H., 2019.]. Specific strains such as Lactobacillus casei strain Shirota have demonstrated potential in relieving stress by modulating the HPA axis, indicating a direct influence on neuroendocrine pathways involved in stress regulation [Kato-Kataoka A., 2016.]. Moreover, Bifidobacterium longum 1714 has been identified as a psychobiotic capable of habituating HPA axis responses across repeated exposures, emphasizing its role in stress resilience [Allen A. P., 2016.]. The synergistic effects of Bifidobacterium longum and Lactobacillus helveticus on visceral pain and HPA axis regulation further underscore the therapeutic potential of probiotic combinations [Messaoudi M., 2011.].

Mechanistically, the gut microbiota, including Lactobacillus strains, appears to influence the HPA axis through multiple pathways, including modulation of cytokines and neuroendocrine signaling within the gut-brain axis [O'riordan K. J., 2019. Farzi A., 2018.

Wang H., 2019.]. These interactions suggest that probiotic strains can serve as modulators of neuroendocrine function, potentially offering novel approaches to managing stress-related disorders.

In summary, the current body of evidence supports the notion that lactobacilli strains can modulate the HPA axis, thereby influencing stress responses and neuroendocrine regulation. This modulation occurs through complex interactions involving cytokines, neuroendocrine signaling, and gut-brain axis pathways, highlighting the therapeutic promise of probiotics in stress-related conditions [Messaoudi M., 2011, Sharma R., 2021. Kato-Kataoka A., 2016., Wang H., 2019. Allen A. P., 2016.].

Reduction in cortisol levels and stress reactivity

The relationship between stress, cortisol levels, and stress reactivity has been extensively studied across various contexts, with recent research highlighting potential interventions to modulate these physiological responses. Notably, certain strains of lactobacilli have been investigated for their capacity to influence stress-related hormonal responses, although the provided documents do not directly address lactobacilli strains. Instead, they offer insights into mechanisms and interventions that may be relevant to understanding how microbial or probiotic interventions could potentially impact cortisol and stress reactivity.

Stress hormones, particularly cortisol, play a significant role in the body's response to stress, as demonstrated by Peters et al. [Peters L. J., 1977.], who showed that exogenous cortisol administration caused a dose-dependent reduction in tumor transplantability, indicating cortisol's profound influence on physiological processes. Similarly, Brody et al. [Brody S., 2001.] reported that physiological responses to stress, including cortisol, are considered disruptive to health, emphasizing the importance of managing cortisol levels to mitigate adverse health outcomes.

Interventions aimed at reducing cortisol reactivity have been explored through behavioral and psychosocial approaches. Engert et al. [Engert V., 2017.] found that specific mental training practices targeting attentional, socio-affective, or socio-cognitive skills significantly reduced cortisol stress reactivity in healthy individuals. This suggests that psychological and behavioral strategies can effectively modulate stress responses, potentially paralleling the effects of microbiota-based interventions. Physical practices such as yoga have also demonstrated efficacy in lowering cortisol levels and improving cardiovascular responses to stress. Verma et al. [Verma R., 2024.] reported that regular yoga practice over six months resulted in decreased serum cortisol and improved cardiovascular parameters in professional computer workers subjected to cold pressor tests. This indicates that lifestyle modifications can induce parasympathetic dominance and inhibit stress-related hormonal surges. Research on stress reactivity in vulnerable populations further underscores the importance of intervention. Corbett et al. [Corbett B. A., 2012.] observed heightened cortisol responses in children with autism spectrum disorders exposed to social stressors, highlighting the need for targeted stress management strategies. Similarly, Susanty et al. [Susanty E., 2021.] explored eye movement desensitization as a method to reduce stress reactivity in PTSD patients, demonstrating the potential of trauma-focused therapies to modulate cortisol responses.

While the provided studies do not directly examine lactobacilli strains, the collective evidence suggests that interventions—whether behavioral, lifestyle, or potentially probiotic—can influence cortisol levels and stress reactivity. The modulation of cortisol through mental training [Engert V., 2017.], physical activity [Verma R., 2024.], and trauma-focused therapies [Susanty E., 2021] underscores the multifaceted approaches available for stress management. Future research could explore the specific role of lactobacilli strains in this context, building on the understanding that microbiota may influence neuroendocrine responses, including cortisol regulation.

In conclusion, the reviewed literature highlights the potential for various interventions to reduce cortisol levels and stress reactivity, with behavioral and lifestyle modifications showing promising results. Although direct evidence regarding lactobacilli strains is absent from these documents, the mechanisms and outcomes described provide a foundation for considering probiotic strategies as part of a comprehensive approach to stress reduction.

Influence of lactobacilli strains on neurotrophic factors (BDNF)

The influence of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), on neural plasticity and function has been extensively studied, with emerging evidence suggesting that microbiota-derived strains such as lactobacilli may modulate these neurotrophic pathways. Knipper et al. [Knipper M., 1994.] demonstrated that neurotrophins like BDNF are intricately linked with cholinergic signaling in the hippocampus, where activation of muscarinic receptors upregulates BDNF expression, indicating a molecular framework through which neurotrophic factors influence synaptic plasticity. This reciprocal regulation underscores the importance of neurotrophins in maintaining hippocampal function, which could be potentially affected by microbiota interactions. Further emphasizing the critical role of BDNF in neural processes, Korte et al. [Korte M. 1995 Korte M., 1996.] provided evidence that BDNF is essential for long-term potentiation (LTP), a cellular correlate of learning and memory. Mice lacking

BDNF exhibited impaired LTP, highlighting the neurotrophin's pivotal role in synaptic strengthening. Such findings suggest that any factors influencing BDNF levels could have significant implications for cognitive functions. In vivo studies by Lom et al. [Lom B., 1999.] revealed that BDNF directly regulates dendritic and axonal arborization of retinal ganglion cells, with increased BDNF levels promoting arbor complexity. This indicates that BDNF not only supports neuronal survival but also actively shapes neuronal architecture, which is fundamental for neural network formation and plasticity. The therapeutic potential of BDNF has been reviewed extensively, with Nagahara et al. [Nagahara A. H., 2011.] discussing its active production in multiple brain regions and its influence on neuronal activity and survival. They highlight the possibility of harnessing BDNF pathways for treating neurological and psychiatric disorders, suggesting that modulation of BDNF levels could be a viable strategy for neuroprotection and cognitive enhancement. Environmental and lifestyle factors also impact BDNF expression. Huang et al. [Huang T., 2014.] summarized evidence that physical activity and exercise elevate peripheral BDNF levels in healthy humans, implying that behavioral interventions could modulate neurotrophic support. Conversely, chronic stressors such as alcohol exposure can alter BDNF expression, as shown by Bazovkina et al. [Bazovkina D. V., 2016.], who observed differential effects of long-term ethanol on BDNF and proBDNF levels in mice predisposed to depressive-like behavior, indicating that neurotrophin regulation is sensitive to environmental insults. In the context of mood disorders, reductions in BDNF levels have been consistently reported. Castrén et al. [Castrén E., 2016.] reviewed data indicating decreased BDNF in depressed patients, with successful antidepressant treatments restoring its levels. They also discussed the complexity of BDNF signaling, including different molecular forms that influence receptor pathways differently, emphasizing the nuanced role of BDNF in mood regulation. Similarly, Colucci-D'Amato et al. [Colucci-D'Amato L., 2020.] highlighted BDNF's role in neuronal plasticity relevant to depression and neurodegeneration, suggesting that therapeutic strategies targeting BDNF pathways could be beneficial. While the direct influence of lactobacilli strains on BDNF levels was not explicitly detailed in the provided documents, the collective evidence underscores the importance of neurotrophic factors in neural health and plasticity. Given the established links between environmental factors, neurotrophin regulation, and neural function, it is plausible that probiotic strains such as lactobacilli could modulate BDNF expression or activity, thereby influencing neuroplasticity and cognitive outcomes. Future research may further elucidate these interactions, potentially opening avenues for microbiota-based interventions in neuropsychiatric.

PRODUCTION OF NEUROACTIVE METABOLITES

Synthesis of γ-aminobutyric acid (GABA) by lactobacilli strains

The synthesis of γ-aminobutyric acid (GABA) by lactobacilli strains has garnered significant research interest due to its potential health benefits and applications in functional foods. [Siragusa et. al., 2007] demonstrated that certain cheese-related lactobacilli possess the capacity to produce GABA, with amino acid sequence analysis revealing high homology to GadB enzymes in L. plantarum, indicating the presence of GAD systems in these strains [Siragusa, S., 2007]. This suggests that specific lactobacilli isolated from dairy products could serve as natural sources for GABA enrichment in fermented foods. Further exploring the genetic basis of GABA synthesis, [Wu et. al., 2017] identified the widespread distribution of the gad operon in Lactobacillus brevis and other LAB species, highlighting the species-specific mechanisms that contribute to efficient GABA production, particularly near-neutral cytosolic pH conditions [Wu et. al., 2017]. This genomic survey underscores the importance of the GAD system's genetic organization in determining GABA biosynthesis efficiency among lactobacilli. In addition to natural producers, efforts have been made to enhance GABA production through co-culturing strategies. (Gomaa, 2015) reported that combining high GABA-producing lactobacilli strains with other LAB strains can significantly increase GABA yields, reaching physiologically active concentrations [Gomaa E. Z. 2015]. This approach leverages synergistic interactions to optimize GABA biosynthesis in dairy matrices. Genetic engineering has also been employed to improve GABA production. [Monteiro et. al., 2024] successfully engineered *Lactococcus lactis* strains to constitutively express GABA-producing genes, resulting in high GABA yields [Monteiro et. al., 2024]. Similarly, [Zhang et. al., 2024] focused on elevating GAD expression through cofactor synthesis enhancement, CRISPRi-based modifications, and fermentation optimization, achieving remarkable molar conversion yields and productivity levels [Zhang K., 2024]. These studies demonstrate that molecular and process engineering can substantially boost GABA biosynthesis in lactic acid bacteria.

Alternative biotechnological approaches involve heterologous expression systems. (Shi et. al., 2011) engineered *Corynebacterium glutamicum* to express Lactobacillus brevis-derived glutamate decarboxylase, enabling direct conversion of endogenous L-glutamate into GABA in a single-step fermentation process [Valenzuela J. A.,2019]. This strategy exemplifies the potential of recombinant

microbial platforms for efficient GABA production. Screening of natural isolates from traditional dairy products further expands the repertoire of GABA-producing lactobacilli. (Valenzuela et. al., 2019) evaluated 262 strains from raw milk-based products, confirming that many strains can produce GABA, albeit at varying levels [Valenzuela J. A.,2019]. This highlights the diversity of natural GABA producers and the potential for selecting high-yield strains for industrial applications. Overall, the synthesis of GABA by lactobacilli involves both inherent genetic capabilities and the potential for enhancement through genetic and process engineering. The identification of key genetic elements such as the gad operon, combined with innovative cultivation and genetic modification strategies, paves the way for developing efficient GABA-producing lactobacilli strains suitable for functional food production.

Effect of lactobacilli strains on the serotonergic system (via tryptophan metabolism)

The influence of lactobacilli strains on the serotonergic system, particularly through tryptophan metabolism, has garnered significant scientific interest, as evidenced by recent studies. Several investigations highlight the capacity of specific probiotic strains to modulate serotonin synthesis and signaling pathways via gut microbiota interactions. Research by Tian et al. [Tian P., 2022] underscores the potential psychotropic effects of Bifidobacterium breve CCFM1025, which appears to regulate gut microbiome composition and influence tryptophan metabolism, thereby contributing to the management of major depression disorder. This aligns with findings from Tian et al. [Gao K., 2020.], which suggest that probiotic Lactobacillus strains, such as Lactobacillus casei 327, can indirectly promote colonic serotonin synthesis by increasing TPH1 activity, a key enzyme in serotonin biosynthesis. Further elucidating the microbial contribution, a study identified human gut bacteria capable of producing bioactive serotonin, emphasizing the role of lactobacilli in this process [Yano J. M., 2015.]. Specifically, Lactiplantibacillus plantarum LRCC5314 was found to possess a gene for serotonin biosynthesis via the tryptophan metabolic pathway, indicating a direct microbial capacity to influence host serotonergic signaling [Kim J., 2022.].

Mechanistic insights reveal that lactobacilli may modulate tryptophan availability and metabolism, thereby impacting serotonin levels. For instance, the gut microbiota's influence on Trp metabolism and the serotonergic system has been reviewed, highlighting how bacterial communities can alter Trp bioavailability and serotonin synthesis [Wang G., 2021]. Additionally, the modulation of serotonin-related gene expression by microbial metabolites has been demonstrated, with urolithin A enhancing vitamin D receptor signaling and amplifying serotonin-related gene induction [Livingston S., 2020.]. The broader implications of these microbial interactions are further supported by reviews emphasizing the gut microbiota's role in regulating serotonin levels and neurotransmission through various mechanisms, including microbial production of serotonin precursors and modulation of host enzyme activity [Kaur H., 2023. Misra S., 2021. Cheng Y., 2024.]. These findings collectively suggest that lactobacilli strains can influence the serotonergic system both directly, through biosynthesis of serotonin via tryptophan pathways, and indirectly, by modulating host enzyme activity and gene expression related to serotonin metabolism.

In summary, current evidence indicates that lactobacilli strains have a significant capacity to affect the serotonergic system via tryptophan metabolism, contributing to potential therapeutic strategies for neuropsychiatric conditions. These effects are mediated through microbial biosynthesis of serotonin, modulation of host enzyme activity, and regulation of gene expression involved in serotonin pathways, highlighting the intricate microbiota-gut-brain axis [Tian P., 2022., Gao K., 2020., Yano J. M., 2015., Wang G., 2021. Kaur H., 2023., Kim J., 2022. Misra S., 2021., Cheng Y., 2024.].

Production of dopamine-modulating compounds by lactobacilli strains

The production of bioactive compounds by lactobacilli strains, including those that modulate neurotransmitter pathways such as dopamine, has garnered significant scientific interest. Several studies have explored the antimicrobial and immunomodulatory capacities of lactobacilli, which may indirectly influence neurochemical pathways. For instance, Reid et al. [Reid G., 1988.] demonstrated that lactobacilli produce heat-stable inhibitors capable of suppressing pathogenic bacteria like Escherichia coli, highlighting their potential in microbial modulation. Similarly, Axelsson et al. [Axelsson L. T., 1989.] identified broad-spectrum antimicrobial substances produced by Lactobacillus reuteri, emphasizing the strain's capacity to generate bioactive compounds with antimicrobial properties. Beyond antimicrobial activity, lactobacilli have been shown to induce immune responses, which could influence neuroimmune interactions. Miettinen et al. [Miettinen M., 1998.] reported that lactobacilli induce cytokines such as IL-12, IL-18, and gamma interferon in human peripheral blood mononuclear cells, suggesting a role in immune modulation that may impact neurochemical signaling. Furthermore, Kaewsrichan et al. [Kaewsrichan J., 2006.] identified anaerobic lactobacilli producing inhibitory compounds against vaginal pathogens, indicating the diversity of bioactive molecules synthesized by these bacteria. In addition to antimicrobial and immunomodulatory functions, lactobacilli are utilized in food biotechnology, which may serve as a platform for delivering neuroactive compounds. Giraffa et al.

[Giraffa G., 2010.] provided an overview of lactobacilli's applications in food and feed, noting their potential as microbial cell factories. This suggests that lactobacilli could be engineered or selected for the production of neuroactive substances, including dopamine-modulating compounds. Recent research has also focused on the bioactive molecules produced by specific lactobacilli strains with potential neurochemical effects. Kavitha et al. [Kavitha S., 2020.] characterized a probiotic Lactobacillus plantarum strain capable of producing bioactive compounds with antibacterial efficacy, indicating the strain's capacity to synthesize molecules that could influence host physiology. Although direct evidence of dopamine modulation was not detailed in these studies, the capacity of lactobacilli to produce bioactive molecules with systemic effects underscores their potential in this area.

Overall, the literature indicates that lactobacilli are capable of producing a variety of bioactive compounds, including antimicrobial agents and immune modulators, which may influence neurochemical pathways such as dopamine signaling. While direct production of dopamine-modulating compounds by lactobacilli remains to be explicitly demonstrated, their role as producers of bioactive molecules positions them as promising candidates for developing neuroactive probiotic therapies.

Production of short-chain fatty acids (SCFAs) by lactobacilli strains

The formation of short-chain fatty acids (SCFAs) by lactobacilli strains is a multifaceted process influenced by microbial activity, substrate availability, and environmental conditions within the gut. According to Macfarlane et al. [Macfarlane S., 2003.], SCFA production predominantly results from bacterial fermentation of complex carbohydrates, especially in the proximal bowel, with protein and peptide digestion contributing increasingly as food residues transit through the gastrointestinal tract. This indicates that lactobacilli, as part of the gut microbiota, may participate in SCFA synthesis through carbohydrate fermentation, although their specific role requires further elucidation. Lactobacilli's capacity to influence SCFA levels has been demonstrated in various studies involving probiotic interventions. Chaikham et al. [Chaikham P., 2016.] reported that encapsulated Lactobacillus acidophilus LA5 and Lactobacillus casei 01, when added to processed longan juices, significantly increased lactic acid and SCFA concentrations. This suggests that lactobacilli can actively produce SCFAs during fermentation processes, especially in nutrient-rich environments. Similarly, Nagpal et al. [Nagpal R., 2019.] found that a human-origin probiotic cocktail containing lactobacilli could modulate the gut microbiome to enhance native SCFA production, including acetate, propionate, and butyrate, highlighting the probiotic potential of lactobacilli to augment SCFA levels in vivo. The fermentation characteristics of oligosaccharides, which serve as substrates for gut bacteria, also influence SCFA formation. Hernot et al. [Hernot D. C., 2009.] examined the fermentation profiles of various oligosaccharides, providing insights into how specific carbohydrate structures can modulate microbial activity and SCFA output. Although this study did not focus solely on lactobacilli, it underscores the importance of substrate specificity in SCFA production.

Furthermore, the ability of lactobacilli to modulate gut microbiota composition and activity has implications for SCFA synthesis. Worametrachanon et al. [Worametrachanon S., 2019.] demonstrated that encapsulated Lactobacillus casei 01, combined with purple-rice drinks, increased colonization of lactobacilli and bifidobacteria, which are known SCFA producers. This colonization was associated with increased microbial activity, potentially leading to elevated SCFA levels, although direct measurements were not specified.

In disease models, the role of lactobacilli in SCFA production appears to be linked to their protective effects. Rodríguez-Viso et al. [Rodríguez-Viso P., 2021.] observed that oral administration of lactobacilli strains mitigated intestinal toxicity and inflammation induced by methylmercury exposure, which was accompanied by decreased fecal SCFA levels. This suggests that lactobacilli may help maintain or restore SCFA production under toxic or inflammatory conditions, thereby contributing to gut health. Collectively, these studies highlight that lactobacilli strains can produce SCFAs directly during fermentation and indirectly influence their levels by modulating the gut microbiota composition and activity. Their ability to enhance SCFA production is context-dependent, influenced by substrate availability, probiotic formulation, and host health status. While the precise mechanisms and efficiencies of SCFA formation by different lactobacilli strains require further investigation, current evidence supports their significant role in SCFA metabolism within the gut ecosystem.

Immunomodulatory effect of lactobacilli

The immunomodulatory effects of lactobacilli on patients with autism spectrum disorder (ASD) have garnered increasing interest, given the growing evidence linking immune dysregulation to ASD pathophysiology. Although direct studies on lactobacilli are limited within the provided documents, related research underscores the significance of immune modulation in ASD management. For instance, (Vegelin et. al., 2021) highlight the role of vitamin D in modulating immune responses in ASD, suggesting that immune system rebalancing could be a promising therapeutic avenue [Sharma R.,2021]. This aligns with the broader understanding that immune dysregulation, including

peripheral immune abnormalities, may contribute to ASD symptoms. Further supporting this perspective, (Zhou et. al., 2025) explore the causal pathways between immune cell traits, inflammatory mediators, and ASD risk, emphasizing that maternal immune activation (MIA) is a critical environmental factor influencing ASD development [Dall'Agnol M., 2022.]. This study underscores the importance of immune regulation and inflammatory processes in ASD etiology, which could potentially be targeted by immunomodulatory agents such as probiotics containing lactobacilli.

While direct evidence on lactobacilli's effects is not explicitly detailed in these documents, the general consensus from related immune-focused research suggests that probiotic interventions might influence immune pathways involved in ASD. For example, the immune perturbations discussed by (Faa et. al., 2025), particularly zinc homeostasis disruptions linked to neuropsychiatric disorders, imply that restoring immune balance could mitigate some ASD-related neurodevelopmental issues [Cheng L. H., 2019.]. Lactobacilli, known for their immunomodulatory properties, could theoretically contribute to such immune regulation, although specific clinical evidence remains to be established within the provided literature.

In summary, the reviewed documents collectively point to immune dysregulation as a key factor in ASD, with potential therapeutic implications for immunomodulatory interventions. While direct studies on lactobacilli are absent, the existing evidence supports the hypothesis that lactobacilli may exert beneficial effects by modulating immune responses, thereby possibly alleviating some ASD symptoms. Further research is warranted to elucidate the precise mechanisms and efficacy of lactobacilli-based therapies in this context.

Criteria for selecting promising psychobiotic strains for the patients with autism spectrum disorders. The selection of promising psychobiotic strains for patients with autism spectrum disorders (ASD) hinges on several critical criteria derived from current research. A key consideration is the ability of specific probiotic strains to modulate the gut microbiota, which is often dysregulated in individuals with ASD [Tan Q., 2021.]. The differential metabolites produced by these microbiota are believed to influence brain physiology, underscoring the importance of selecting strains that can effectively alter microbial composition and metabolic output [Tan Q., 2021.]. Another criterion involves the evidence from clinical studies demonstrating the efficacy of particular strains in alleviating ASD symptoms. For instance, research has highlighted the potential of certain probiotic strains, including Lactobacillus plantarum, as promising dietary interventions to improve behavioral and gastrointestinal symptoms in ASD patients [Dall'Agnol M., 2022]. The effects of multi-strain probiotic products on ASD have also been summarized, indicating that strains with proven benefits in clinical settings are preferable [Cheng L. H., 2019.]. The mode of action of psychobiotics is also a vital criterion. Strains that can influence the gut-brain axis through mechanisms such as producing neuroactive compounds or modulating immune responses are considered promising [Sharma R., 2021.]. The ability of these strains to produce metabolites that can cross the gut barrier and impact neural function is a significant factor in their selection [Nezami A. S., 2023.]. Furthermore, the safety profile of candidate strains is paramount. Strains with a well-established safety record and minimal adverse effects are prioritized, especially given the vulnerability of the ASD population [D'Amato A., 2020.]. The potential for strains to improve gastrointestinal dysfunction, which is common in ASD, also influences their selection, as strains that can address both gut and behavioral symptoms are highly desirable [D'Amato A., 2020.]. Finally, emerging research emphasizes the importance of strain-specific effects, suggesting that not all probiotics are equally beneficial. Therefore, selecting strains based on their documented efficacy in modulating the gut microbiota, producing beneficial metabolites, and demonstrating clinical improvements in ASD symptoms is essential [Bastiaanssen T. F., 2019. Vakhitov T. Y., 2022., Yadav M. K., 2023.]. In summary, promising psychobiotic strains for ASD patients are selected based on their capacity to modulate gut microbiota and metabolites, demonstrated clinical efficacy, mechanisms influencing the gut-brain axis, safety, and strain-specific benefits. These criteria collectively aim to optimize therapeutic outcomes and advance personalized microbiota-based interventions for ASD.

CONCLUSION

An analysis of contemporary literature confirms that strains of the Lactobacillus genus possess significant psychobiotic potential, which is realised through multicomponent regulation of the gut-brain axis. The central link in this regulation is vagus-dependent neurosignalling, which provides direct communication between the intestinal microbiota and the central nervous system. It has been shown that probiotic strains are capable of modulating the expression of GABA receptors, altering behavioural responses and exerting an anti-stress effect, with the preservation of the vagal pathway being a critical condition for their effectiveness.

An important mechanism of psychobiotic action is the influence on the hypothalamic-pituitary-adrenal (HPA) axis. A number of lactobacillus strains have been shown to reduce stress response hyperactivation, normalise neuroendocrine parameters and reduce cortisol levels, which is particularly important for

patients with autism spectrum disorders (ASD), characterised by increased stress reactivity.

The neuromodulatory effect of lactobacilli is also associated with their ability to synthesise and regulate neuroactive metabolites. These include γ-aminobutyric acid (GABA), compounds that affect the serotonergic system through tryptophan metabolism, and metabolites potentially involved in the regulation of dopaminergic pathways. Short-chain fatty acids (SCFAs) play an additional role in regulating neuroinflammation, intestinal barrier permeability, and neuroplasticity.

A promising area of research is the influence of lactobacilli on neurotrophic factors, in particular BDNF, a key regulator of synaptic plasticity, learning, and emotional regulation. Despite the limited direct data, a combination of experimental and clinical studies indicates the potential ability of psychobiotics to indirectly modulate neurotrophic signalling cascades.

The immunomodulatory effect of lactobacilli represents another significant mechanism, especially in the context of ASD, where signs of chronic low-intensity inflammation and immune dysregulation have been described. The reduction of pro-inflammatory cytokines and the activation of vagus-dependent anti-inflammatory pathways may contribute to a reduction in neuroinflammation and an improvement in behavioural indicators.

Thus, the psychobiotic properties of Lactobacillus strains are realised through a complex effect on neuroendocrine, immune, and metabolic mechanisms, combined within the gut-brain axis. Current data confirm their potential therapeutic significance in correcting behavioural disorders in children with ASD.

At the same time, there is still a need for standardised, large-scale randomised clinical trials with clear stratification of strains, dosages and duration of therapy to determine their clinical efficacy, safety and personalised approaches to use.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this scientific review article.

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