The Effectiveness of Probiotics as Adjuvant Therapy in Children with Autism Spectrum Disorder: A Literature Review

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex developmental disorder associated with gastrointestinal and neuropsychological disturbances. The growing understanding of the gut microbiota role via the gut–brain axis has opened opportunities for using probiotics as adjuvant therapy in managing ASD. This literature review aims to evaluate the effectiveness of *Lactobacillus* probiotics as adjunct therapy in children with ASD. A systematic literature search was conducted using the PICO framework and relevant keywords for sources published between 2021 and 2025. Of 22 screened articles, eight studies met the inclusion criteria and were analyzed. Results suggest that *Lactobacillus* probiotics show promising effects as adjunct therapy in ASD management. They help restore gut microbiota balance, increase beneficial species such as *Bifidobacterium longum* and *Lactobacillus* spp., and reduce gastrointestinal symptoms including diarrhea and constipation. Neuropsychological improvements include enhanced social responsiveness and reduced anxiety, mediated by microbiota modulation, neuroactive metabolites, and immune system regulation. Additionally, probiotics support neurocognitive and behavioral enhancements via the gut–brain axis, measurable through EEG biomarkers. Minimal side effects and a high safety profile make probiotics a safe and feasible adjunct to conventional treatment. In conclusion, probiotics have potential as a sustainable supportive therapy; however, further high-quality studies with longer durations are required to confirm clinical benefits and fully understand the underlying mechanisms.

Keyword : Autism spectrum disorders; gut-brain axis; *Lactobacillus*; probiotic

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent difficulties in social interaction and communication, along with restricted and repetitive patterns of behavior or interests[1]. ASD frequently co-occurs with other conditions, including intellectual disability, attention deficit/hyperactivity disorder (ADHD), and specific learning disorders[2]. Although diagnosis before 12 months of age is challenging, it is typically possible by two years of age. Symptoms emerge in early childhood and often persist through adolescence and adulthood[3].

Multiple prenatal and perinatal factors have been associated with an increased risk of ASD, including low birth weight, history of asphyxia, maternal and paternal age at delivery, mode of delivery, maternal race, antidepressant use during pregnancy, exposure to cigarette smoke, maternal stress, parity, maternal bleeding, child's sex, early complementary feeding (before six months), and maternal infection during pregnancy. These factors may directly or indirectly disrupt fetal brain development, contributing to the pathogenesis of ASD[4].

Globally, the World Health Organization (WHO) estimates the average prevalence of ASD at approximately 1% of the pediatric population[5]. More recent data from the United States Centers for Disease Control and Prevention (CDC) in 2022 indicate a prevalence of 1 in 44 children. In Indonesia, with an estimated population of 270.2 million children in 2021, approximately 3.2 million children were reported to have ASD[6]. The disorder is significantly more common in males, with a male-to-female ratio of approximately 4:1, which may reflect differences in genetic vulnerability or diagnostic bias[7].

Children with ASD frequently experience gastrointestinal disturbances. These symptoms are linked to dysfunction of the gut brain axis, a bidirectional communication system between the intestine and the central nervous system that influences brain function and behavior[8]. Individuals with ASD often exhibit increased intestinal permeability ("leaky gut"), allowing greater passage of foreign substances, as well as impaired activity of digestive enzymes such as dipeptidyl peptidase-IV (DPP-IV), which is involved in the breakdown of gluten and casein proteins. Collectively, these factors may exacerbate neuropsychiatric symptoms in children with ASD[9]. Consequently, comprehensive management of ASD should address gastrointestinal aspects to improve overall quality of life and treatment outcomes.

Probiotics have emerged as a potential adjunctive therapy for managing gastrointestinal symptoms in ASD. Understanding the gut brain axis provides a rationale that oral probiotic administration may alleviate ASD-related symptoms through modulation of

the gut microbiota. Both in vitro and in vivo studies have demonstrated a specific role for gut microbiota in brain development and function[10]. Therefore, probiotic therapy is currently an active area of research. This literature review aims to evaluate the effectiveness of probiotics as adjunct therapy in children with ASD.

Material and Methods

The method used was a search of various literature sources discussing the effectiveness of probiotic use as adjuvant therapy in children with ASD. The PICO method was used to facilitate the search for literature to be used as references. PICO consists of four parts, namely Population, Intervention, Comparison, and Outcome.11 A combination of several terms from the PICO framework was used to search for literature relevant to the study, as follows:

Population: Patients with Autism Spectrum Disorders (ASD)

Intervention: *Lactobacillus* probiotics

Comparison: Placebo

Outcome: Effectiveness of probiotic use as adjuvant therapy in children with ASD

Literature sources were obtained from Scopus, Sciencedirect, Mendeley, Proquest, and Pubmed with searches conducted in English. Based on the type of publication, we used scientific literature relevant to the publication period between 2021 and 2025. The keywords used were “Probiotic” AND ‘autism’ AND “ *Lactobacillus*”. Keyword searches were performed using the Boolean Operator method. The data used based on the literature search results included titles, abstracts, methods, and results. A total of 22 journals were deemed eligible and were further screened using the inclusion and exclusion criteria of this study. The inclusion criteria were articles with open access, experimental methods, human samples, and *Lactobacillus* probiotics. Meanwhile, the exclusion criteria for the journals obtained included non-research journals, restricted access, animal samples, and therapies other than *Lactobacillus* probiotics. Eight English-language journals were obtained and further analyzed in this study.

Results

Pharmacokinetics and Pharmacodynamics

Probiotics work in the body through four stages, namely absorption, distribution, metabolism, and excretion. Probiotics are absorbed in the intestinal lumen. Probiotics settle in specific areas and interact with the local microflora and intestinal mucosa[12]. Probiotics

are not significantly metabolized like chemical drugs, but they can influence the metabolism of other microbiota and enzyme activity in the intestine. Probiotic microorganisms are excreted through feces, and their presence can be influenced by factors such as diet and gastrointestinal conditions[13].

The pharmacodynamics of probiotics include their mechanism of action in the body, primarily through modulation of the intestinal microbiota. Probiotics help increase the population of good bacteria such as *Lactobacillus* and *Bifidobacterium*, and suppress the growth of pathogens. Probiotics can increase or decrease the expression of important enzymes such as glutathione-S-transferases (GSTs) and cytochrome P450 (CYP). Additionally, probiotics also improve intestinal barrier function, thereby helping to control drug absorption levels and prevent the translocation of microbes or toxic substances into the systemic circulation[14].

Changes in Brain Activity and Function

Changes in brain activity and function in children with ASD due to probiotic administration have been studied in several studies using various approaches. One study that directly used electroencephalography (EEG) found that after probiotic intervention, there was a decrease in beta and gamma wave activity, which is usually excessive in children with ASD, as well as an increase in interregional brain coherence. These findings were interpreted as an indication of improved connectivity and normalization of electrical activity patterns toward a neurotypical child profile, which has the potential to improve cognitive and behavioral function[15].

Another study showed that psychobiotics such as *Lactobacillus* plantarum and L. *reuteri* can influence brain function through the production of neuroactive metabolites, with effects observed in improved social responses, reduced anxiety, and increased cognitive scores based on clinical assessments such as ATEC and CARS, although no EEG data were provided.[16] Improvements in brain function are also discussed in studies noting enhanced adaptive behavior and communication skills as a result of gut–brain axis mechanisms involving the microbiota's influence on the immune and central nervous systems.[17] Additionally, the PS128 strain was reported to be able to modulate dopamine and serotonin in the brain, which is associated with improvements in anxiety and hyperactivity symptoms, although without direct EEG measurements.[18] References to the default mode network as a potential pathway for the relationship between the microbiota and the brain has also been found, although studies have focused more on behavioral changes and executive function.[19]

Improvements in gastrointestinal and behavioral symptoms are also considered to reflect

changes in brain function through immune, vagal, and neuroendocrine pathways, although no observations were made[20,21]. Meanwhile, the focus on gut microbiota composition without observing brain activity still raises the potential link between microbiota and behavioral symptoms[22]. Overall, although only a few studies explicitly use EEG, most of the literature shows a positive impact of probiotics on the cognitive function and behavior of children with ASD through neurophysiological, immunological, and neurochemical approaches.

The Relationship Between Microbiota and Gastrointestinal Clinical Symptoms

Children with ASD not only experience neurodevelopmental disorders, but also often show gastrointestinal (GI) symptoms such as constipation, diarrhea, flatulence, unusual stool odor, and abdominal pain. These symptoms are reported to occur in more than 80% of children with ASD, as seen in studies by Darwesh et al., 2024 and Meguid et al., 2022[16,20]. One of the main mechanisms explaining this relationship is a disturbance in the composition of the gut microbiota or dysbiosis. Results indicate that probiotics can increase the presence of species such as Streptococcus thermophilus, *Bifidobacterium* longum, *Lactobacillus* salivarius, *Bifidobacterium* spp., and *Lactobacillus* spp., which play a role in the digestive system[17,20]. Improvement in GI symptoms was also observed in patients, such as a reduction in the severity of diarrhea, constipation, number of bowel movements, and a change in stool consistency to a softer consistency. This indicates success in improving the balance of gut microbiota in ASD patients.

Neuropsychological Effects

The effects of probiotics on the neuropsychological aspects of children with ASD have been extensively studied and show promising results. Probiotic supplementation has been shown to alter brain electrical activity measured via EEG, with increased coherence at gamma and beta frequencies associated with reduced repetitive behaviors and improved social skills. Adjustments in brain lateralization have also been found to support improvements in social interaction, communication, and sleep quality through the gut–brain axis[15]. Similarly, psychobiotics such as *Lactobacillus* plantarum and L. reuteri have been reported to improve social responses, reduce anxiety, and enhance emotional regulation. Some strains, such as *Lactobacillus* gasseri CP2305, also play a role in providing relaxation effects and improving sleep quality[16]. These findings are reinforced by documentation of improvements in maladaptive behavior, receptive language, and reduced stress in parents of children with ASD who were given probiotics[17].

Strain PS128 has also been reported to play a role in lowering anxious/depressed

subscale scores based on ASEBA, indicating potential benefits for emotional stability, although this has not been accompanied by direct evaluation of social function or sleep. Children with ASD and/or ADHD who consumed probiotics also showed significant improvement in hyperactivity and impulsivity, especially at an early age, although this was not followed by significant changes in social functioning or sleep[19]. Another study noted improvements in communication, adaptive skills, reduced anxiety, and sleep quality after three months of probiotic supplementation[20]. Although it did not explicitly evaluate psychological or sleep aspects, there were significant improvements in global functioning and communication and sleep quality after three months of probiotic supplementation[20]. Although not explicitly evaluating psychological or sleep aspects, there were significant improvements in global function and communication[21]. Meanwhile, conceptual studies discuss the possible link between microbiota and ASD neuropsychological symptoms through a synthesis of previous studies[22].

Overall, although the strength of evidence varies between studies, most of the literature suggests that probiotics and psychobiotics can provide benefits for behavioral, emotional, sleep quality, psychological, and social aspects of children with ASD. These effects are thought to be mediated by gut microbiota modulation, neuroactive metabolites, the immune system, and the gut–brain axis pathway, and in some cases are supported by objective evidence such as EEG results

Discussion

Side Effects of Therapy

Overall studies state that the use of probiotics as an adjunct therapy in children with ASD does not cause side effects. Probiotics are considered a non-invasive intervention with a high safety profile. Additionally, probiotics do not negatively interact with the pharmacological treatments commonly administered to ASD patients, thereby minimizing the risk of drug interactions. Considering the potential benefits for gut microbiota balance and improvements in gastrointestinal and behavioral symptoms, supported by the very low risk of side effects, probiotics are now considered a promising, safe, and sustainable adjunct therapy in the multidisciplinary management of ASD.

Advantages and Limitations of Journals

Based on the eight journals reviewed, probiotic interventions in children with ASD show promising therapeutic benefits through the gut-brain axis mechanism. The multidimensional approach used by Belleci et al. (2022), Meguid et al. (2022), and Guidetti

et al. (2022) shows that the effects of probiotics are not limited to improving gastrointestinal symptoms, but also impact neuropsychological, behavioral, and even family stress aspects[15,17,20]. Additionally, Belleci et al. (2022) highlight the use of EEG as a biomarker to assess the neurophysiological effects of probiotics, providing objective data that strengthens clinical evidence.[15] Similar findings are also demonstrated by Liu et al. (2023) and Marticella et al. (2025), who emphasized improvements in anxiety, depression, and executive function, especially in early childhood, although limitations such as small sample sizes and short intervention durations remain challenges[18,19].

Meanwhile, Darwesh et al. (2024) and Retuerto et al. (2024) made important contributions in clarifying the gut microbiota profile of children with ASD. They demonstrate an association between microbiota composition (both bacteria and fungi) and the severity of ASD symptoms, although a causal relationship cannot yet be concluded[16,22]. Retuerto et al. (2024), for example, used non-ASD siblings as controls, which helped eliminate genetic and environmental variables, but still did not directly measure neuropsychological effects[22]. This distinguishes this study from Mensi et al. (2021), which was conducted in a real-life setting with a longer follow-up period, adding practical relevance despite methodological weaknesses such as the absence of randomization and a control group, which reduce the strength of the scientific evidence[21].

Although many studies use a randomized controlled trial (RCT) design, such as Liu et al. (2023), Guidetti et al. (2022), and Marticella et al. (2025), nearly all face common limitations such as small sample sizes, population heterogeneity, and reliance on parents' subjective reports[17,18,19]. Additionally, many studies have not assessed long-term effects and remain limited in understanding the specific biological mechanisms of certain probiotic strains. Therefore, although the results are promising, further studies with stronger methodologies, in-depth microbiome analysis, and longer intervention and follow-up durations are needed to strengthen the evidence of the effectiveness and safety of probiotics as adjuvant therapy in ASD.

Therapeutic Potential

Probiotics have great potential as adjuvant therapy for children with ASD in Indonesia, mainly because they are relatively inexpensive and target the gut–brain axis. In the future, local studies need to be conducted to test the effectiveness of probiotic strains available on the Indonesian market, taking into account the microbiota profile of Indonesian children with ASD, which may differ from that of populations in other countries. Research should use a randomized controlled trial (RCT) clinical trial design with an adequate sample size, a

sufficiently long follow-up duration, and combine clinical and microbiota evaluations. Additionally, it is important to assess community acceptance and the integration of probiotics into community-based multimodal interventions.

Conclusion

Probiotics show promising potential as an adjunct therapy for ASD through the gut–brain axis mechanism. Probiotics help improve the balance of gut microbiota, reduce gastrointestinal symptoms, and support improvements in behavior, sleep, and cognitive function. Current research still has methodological limitations such as small sample sizes and short intervention durations, necessitating further studies with stronger designs such as large-scale RCTs, longer intervention duration, and comprehensive evaluation of microbiota changes and their clinical impact to strengthen evidence of probiotic efficacy in children with ASD

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