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Impact of probiotics or synbiotics on symptoms of attention deficit hyperactivity disorder: A systematic review and meta-analysis

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Abstract

Context. Some studies have reported that probiotics and/or prebiotics improve psychiatric symptoms in children with autism spectrum disorder; however, others have found no significant effect of synbiotics on attention deficit hyperactivity disorder (ADHD) symptoms, functionality or comorbid autistic symptoms. The goal of this meta-analysis was to assess the impact of prebiotics or synbiotics on ADHD symptoms.

Evidence Acquisition. PubMed, Scopus, Web of Science, ClinicalTrials.gov, and Google Scholar databases were searched using MeSH terms and keywords. Randomized controlled trials (RCT) investigating the efficacy of the probiotic or synbiotic administration on symptoms of ADHD were selected for the meta-analysis. This search was performed from inception to February 09, 2024. The Comprehensive Meta-Analysis (CMA) V4 software was employed to perform a meta-analysis, calculating standardized mean differences (SMDs) based on sample size, means, and standard deviations from each group. A random-effects model, employing the DerSimonian-Laird approach, and the generic inverse variance weighting method were used to consider research design, treatment duration, and demographic characteristics. The effect sizes were presented as SMD and 95% (CI).

Results. The meta-analysis of five clinical trials, including in total 245 subjects, showed that probiotics or synbiotics supplementation has a significant effect on ADHD symptoms (standardized mean differences: –0.284, 95% CI: –0.552, -0.016, $p<0.001$). The reduction in symptoms of ADHD was robust in the leave-one-out sensitivity analysis.

Conclusion. The consumption of probiotics or synbiotics improves ADHD symptoms.

Keywords. Probiotics; synbiotics; attention deficit hyperactivity disorder; meta-analysis

1. Context

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disturbance, which affects 15.9% of children and adolescents worldwide (1, 2). This neurological disorder is characterized by the presence of cognitive deficit with hyperactivity, impulsivity, and inattention affecting school or work performance, and social and family relationships (3). The role of both genetic and environmental factors has been suggested in

the etiology of this disease (4-7). Patients with ADHD have shown structural abnormalities in the basal ganglia, cerebellum, temporoparietal lobes, corpus callosum, and frontostriatal circuitry, which induce functional and developmental disturbances (8). In this regard, there are various hypotheses about neurobiology dysfunctions involving noradrenergic, dopaminergic, serotoninergic, and cholinergic pathways. The autonomic dysregulation theory includes the alteration of afferent and efferent signaling of the vagus nerve, as well as immune system dysregulation, leading to the development of emotional, behavioral, and cognitive symptoms in ADHD (9). Moreover, there have been growing evidenc eon the role of environmental and certain drug exposure as risk factors for ADHD

Several scales have been developed to assess the severity of ADHD symptoms. Among them, the Conners' Parent Rating Scale is a popular clinical tool that evaluates diagnostic criteria of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), including oppositional, inattention/cognitive problems, hyperactivity/impulsiveness (10). The ADHD Rating Scale-IV is a behavioral questionnaire that obtains information about each ADHD symptom also based on the DSM-IV (11). The Swanson, Nolan, and Pelham-IV (SNAP-IV) parent rating scale includes 18 items, with 9 assessing inattention and 9 assessing hyperactivity/impulsivity. Higher scores indicate more severe ADHD symptoms. SNAP-IV scores are calculated as the average score per item. In the general population, the 95th percentile cutoff is 1.78 for inattention and 1.44 for hyperactivity/impulsivity (12).

The management of patients with ADHD for controlling the core symptoms with pharmacological therapies is complex because of the potential side effects as well as the lack of medical attention due to the stigma of the children´s caregivers for the use of drugs (13). Thus, the use of complementary and alternative therapies for ADHD, such as herbal medicines, vitamins, minerals, and natural supplements, has gained great interest. Among them, probiotic supplementation has demonstrated a reduced risk of developing ADHD, through a favorable impact on cognitive function (14).

The term “probiotics” was used for the first time in 1965 by Lilly and Stillwell as factors produced by one microorganism that induce the growth of another (15). In 1974, Parker redefined this term as “organisms and substances that contribute to intestinal microbial balance” (16). In 1989, Fuller changed the definition of probiotics as “live microbial feed supplement” beneficial to the host animal (17). To date, probiotics are recognized as live microorganisms that may exert health benefits, including inhibition of pathogens, improvement of immune function, metabolic protection, renoprotection, mental health effects, improvement of cancer therapy, and bone health (18-22). On the other hand, in 1995, Gibson and Roberfroid proposed the term synbiotics for “a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria” (23). In 2019, the International Scientific Association for Probiotics and Prebiotics reviewed the definition and scope of synbiotics, including a panel of nutritionists, physiologists, and microbiologists, which updated the definition of synbiotic to “a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host” (24). Therefore, synbiotics are a combination of probiotics and prebiotics that exhibit beneficial effects on the immune system, vitamin synthesis,

and brain activities (25, 26). Certain research indicates that probiotics and/or prebiotics enhance psychiatric symptoms in children diagnosed with autism spectrum disorder (27). Another study found that giving probiotics to babies may lower the chances of developing neuropsychiatric issues like ADHD and Asperger syndrome as they grow up (28). In this regard, in vitro, it has been demonstrated that a group of probiotics produces and delivers some neurotransmitters, including gamma-aminobutyric acid and serotonin, which affect the microbiota–gut–brain axis (29). Furthermore, in vivo studies have revealed that probiotics may improve gastrointestinal function, mood, cognition, and anxiety (30). Some of the bacteria, such as Lactobacillus, Bifidobacterium, B. helveticus, B. longum, B. animalis, Bacillus subtilis, and Enterococcus faecium, have shown probiotic and psychobiotic effects by inducing the synthesis of neurotransmitters in the gut (31-34), leading to regulation the microbiota–gut–brain axis pathways and affecting behavior (35-37). However, a previous randomized controlled trial (RCT) found no significant effect of synbiotics on ADHD symptoms, functionality or comorbid autistic symptoms (12). Otherwise, another study revealed that treatment with synbiotics reduces markers of intestinal and vascular inflammation, such as L12/IL-23p40 and sICAM-1, and increases propionic acid levels in children with ADHD (38). Also, it was suggested that the synbiotic administration improves emotional dysregulation, emotional symptoms, inattention, functioning, and perceived stress levels through the modulation of RANK/RANK-L signaling in adults with ADHD and/or borderline personality disorder and high levels of irritability (39). However, the precise mechanisms involved in the potential beneficial effects of probiotics or synbiotics are uncertain.

Although a previous systematic review examined the beneficial effects of prebiotics, probiotics, and synbiotics on ADHD (40), the meta-analysis was not conducted (41). Additionally, a recent meta-analysis investigated the effectiveness of probiotics for symptoms of ADHD; however, the impact of synbiotics was not considered. Therefore, the goal of this meta-analysis was to assess the impact of prebiotics or synbiotics on ADHD symptoms. The primary objectives are impact of prebiotics or synbiotics on ADHD symptoms.

2. Evidence Acquisition

2.1. Search Strategy

This study was designed and performed according to the PRISMA guidelines (42). The search of articles was conducted in PubMed, Web of Science, Scopus, ClinicalTrials.gov, and Google Scholar databases using the following search terms in titles and abstracts: (“probiotic” OR “probiotics” OR “synbiotics” OR “lactobacillus” OR "bifidobacterium") AND (“attention deficit hyperactivity disorder” OR “attention deficit” OR “hyperactivity” OR “ADHD”) AND (“controlled trial” OR randomized OR “clinical trial” OR trial). The wild-card term ‘‘*’’ was used to improve the search process. This search was performed from inception to February 09, 2024.

2.2. Study Selection

RCTs with either parallel or cross-over design, examining the efficacy of the probiotic or synbiotic administration on attention deficit hyperactivity disorder (ADHD) symptoms, and showing complete outcomes at baseline and the end of follow-up in both intervention and control groups were eligible for meta-analysis. On the other hand, non-randomized trials, uncontrolled trials, RCT without a control group, observational studies, and incomplete outcomes at baseline or the end of the follow-up were exclusion criteria. Independently, AS and LESM performed the screening of articles and the selection of

RCTs, and disagreements were discussed with TJ.

2.3. Data extraction

From the included RCTs, the following information was taken: 1) the initial author's name, 2) the year the study was published, 3) the study design, 4) the kind and dosage of probiotics or synbiotics used, 5) the time frame for administration, 7) the patients' age, gender, and body mass index, and 8) information at the beginning and end of the symptoms of ADHD.

2.4. Quality assessment

The quality of the chosen RCTs was evaluated using the Cochrane criteria, which encompass sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, inadequate outcome data, selective outcome reporting, and additional sources of bias (43). The assessment of each item was categorized as low, unclear, or high risk of bias. The quality assessment was performed by LESM.

2.5. Quantitative Data Synthesis

The Comprehensive Meta-Analysis (CMA) V4 software was employed to perform a meta-analysis, calculating standardized mean differences (SMDs) based on sample size, means, and standard deviations from each group. A random-effects model (using DerSimonian-Laird method) and the general inverse variance weighting technique were employed to account for heterogeneity of publications in terms of study design, features of the populations and treatment duration. The effect sizes were presented as SMD and 95% (CI). The data extraction was performed by TJ and AS. To examine the effect of each study on the overall effect size, we conducted a sensitivity analysis using the leave-one-out strategy (i.e., exclusion of one study at a time to evaluate its impact on the overall result.

2.6. GRADE assessment

The assessment of overall evidence certainty from RCTs was evaluated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines (44). According to the established appraisal criteria, the quality of the evidence was divided into four categories: high, moderate, low, and very low (45).

3. Results

3.1. Study selection process

In summary, 109 articles were obtained after the search in databases, and 98 were removed. Then, 11 full-text articles were checked and six were excluded for incomplete outcomes (n=3), and not including patients with ADHD (n=3). Finally, 5 RCTs were included for meta-analysis. The study selection process is shown in Figure 1. In case where required data were missing or incomplete, attempts were made to contact the corresponding authors to obtain the necessary information. In some cases, relevant data were extracted from published figures using digital extraction methods when possible.

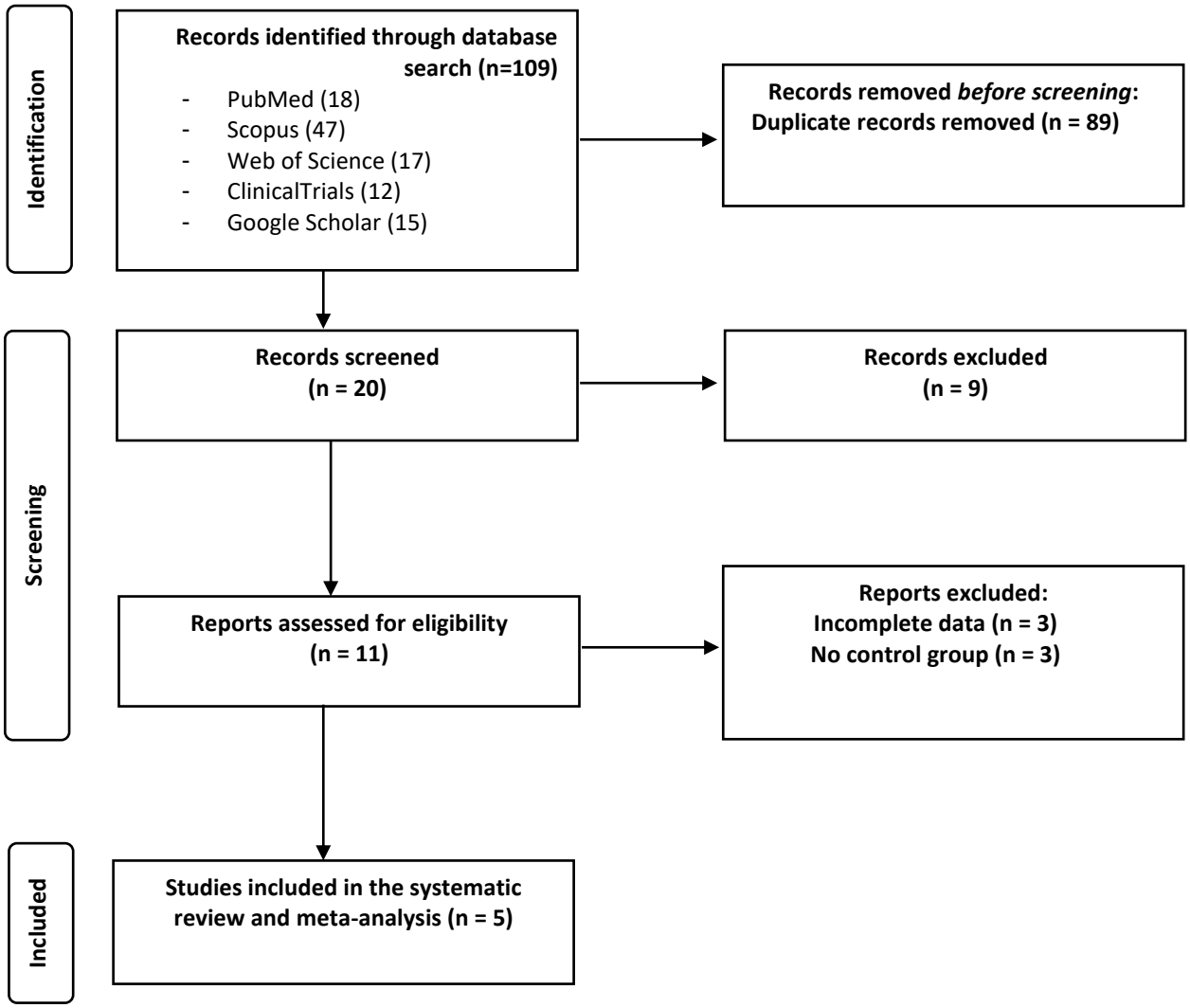

Figure 1. Flow chart of the number of studies selected for meta-analysis

3.2. Characteristics of randomized clinical trials

Data were obtained from five RCT, including in total 245 subjects, of which 133 were in the treatment group and 112 were in the control group. The study by Elhossiny et al. included participants aged 6-16 years, Ghanaatgar et al. aged 6-12 years, Kumperscak et al. aged 4-17 years, Sepehrmanesh al. aged 8-12 years, and Skott et al. aged 5-55 years. Additionally, the study by Elhossiny et al. considered Lactobacillus acidophilus 10 billion CFU twice daily vs. control, Ghanaatgar et al. Bio-Kult-protexin 2x109 CFU daily vs. placebo, Kumperscak et al. Lactobacillus rhamnosus 1010 CFU daily vs. placebo, Sepehrmanesh al. Lactobacillus and Bifidobacterium 8x109 CFU daily vs. placebo, and Skott et al. Synbiotic 2000 4x1011 CFU vs. placebo. Selected studies were published between 2019 and 2023 (12, 46-49). The treatment duration ranged from 8 to 12 weeks. All of the clinical trials had a parallel design. Included clinical trials enrolled children and adolescents with ADHD. Characteristics of the RCT are presented in Table 1.

Table 1. Demographic characteristics of the included studies

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	CPRS-RS	ADHD-RS	SNAP-18	ASRS
Elhossiny et al. 2023	Randomized controlled trial	Children and adolescents	12 weeks	36	*Lactobacillus acidophilus* 10 billion CFU twice daily	*8.7±2.0*	*12 (33)*	19.2±1.0	25.6±4.4	ND	ND	ND
				40	Control	*8.4±1.5*	*13 (32)*	19.8±1.7	25.7±7.6	ND	ND	ND
Ghanaatgar et al. 2022	Randomized, double-blind, placebo-controlled	Children	8 weeks	21	Bio-Kult-protexin 2x10^9 CFU daily	*9.0±1.9*	*4 (19)*	7.6±19.1	60.4±14.4	ND	ND	ND
				17	Placebo	*8.6±1.9*	*8 (47)*	3.5±16.4	46.4±16.4	ND	ND	ND
Kumperscak et al. 2020	Randomized, double-blind, placebo-controlled	Children and adolescents	12 weeks	18	*Lactobacillus rhamnosus* 10^{10} CFU daily	*11.4±3.2*	*6 (33)*	ND	ND	33.7±7.9	ND	ND
				14	Placebo	*12.5±2.3*	*3 (21)*	ND	ND	35.1±10.5	ND	ND
Sepehrmanesh al. 2021	Randomized, double-blind, placebo-controlled	Children	8 weeks	17	Placebo	*8.9±1.0*	*4 (23)*	22.3±6.3	ND	29.6±7.7	ND	ND
				17	Lactobacillus and Bifidobacterium 8x10^9 CFU daily	*9.3±1.3*	*3 (17)*	20.5±6.5	ND	28.3±10.8	ND	ND
Skott et al. 2020	Randomized, double-blind, placebo-controlled	Children and adults	9 weeks	26	Children Placebo	*12 (10-14) **	*18 (26)*	ND	ND	ND	1.55 (1.39,1.83) *	ND
				42	Synbiotic 2000 4x10^{11} CFU				ND	ND	1.54 (1.07,1.94) *	ND
				57	Adults Placebo	*36 (29-42) **	*81 (71)*	23.9 (22.3-26.9) *	ND	ND	ND	ND
				57	Synbiotic 2000 4x10^{11} CFU				ND	ND	ND	ND

Values are expressed as mean ± SD
*Median (IQR)
**Mean only
Abbreviations: CPRS-RS, Conners Parent Rating Scale-short version; ADHD-RS, attention-deficit hyperactivity disorder-rating scale; ND, no data; BMI, body mass index; IQR, interquartile range; HIV, human immunodeficiency virus; SD, standard deviation.

3.3. Quality of bias assessment of clinical trials

Only one study was characterized by a lack of information for random sequence generation, and two clinical trials had insufficient information about allocation concealment. Regarding blinding of participants and personnel, and outcome assessment, only one study showed a high risk of bias for this parameter. Nonetheless, all included RCT exhibited a low risk of bias for incomplete outcome data and selective outcome reporting. The quality of the selected studies is shown in Table 2.

Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Elhossiny et al. 2023	L	L	H	L	L	L
Ghanaatgar et al. 2022	L	U	L	L	L	L
Kumperscak et al. 2020	U	U	U	L	L	U
Sepehrmanesh et al. 2021	L	L	L	L	L	L
Wu et al. 2021	L	L	L	L	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias

3.4. *Effect of probiotics or synbiotics on symptoms of ADHD*

The meta-analysis of 5 clinical trials showed that probiotics or synbiotics supplementation has a significant effect on ADHD (SMD: –0.284, 95% CI: –0.552, -0.016, p<0.001; Figure 2). The reduction in symptoms of ADHD was robust in the leave-one-out sensitivity analysis.

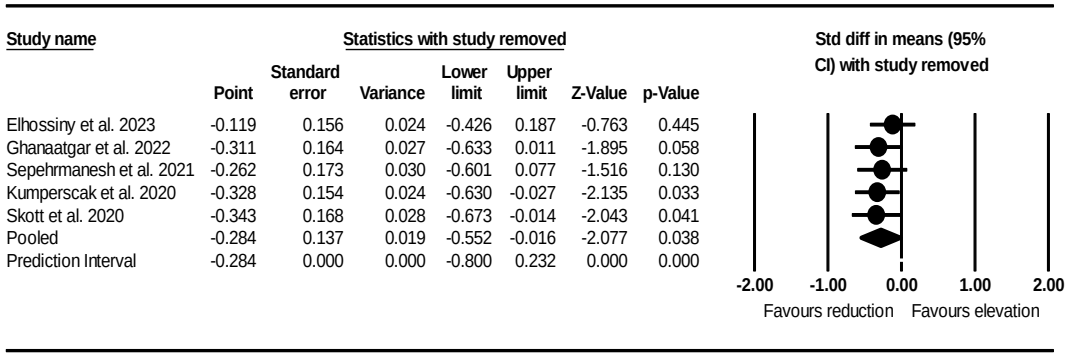

Figure 2. Forest plot representing standardized mean difference and 95% confidence intervals (CIs) for the effect of probiotics or synbiotics on symptoms of attention deficit hyperactivity disorder.

3.5. Subgroup analysis based on assessment tools

In the sub-analyses according to the assessment tools, there was not a significant change in ADHD symptoms (SMD: -0.16, 95% CI: -0.646, 0.326, p=0.519) for ADHD-RS tool and CPRS tool (SMD: -0.432, 95% CI: -1.003, 0.139, p=0.138), separately.

3.6. Grading of Evidence

The quality of evidence for the outcomes was appraised through the GRADE framework. A thorough description of the criteria used for implementing the GRADE tool is shown in Table 3.

Table 3. GRADE approach summary of findings and quality of evidence assessment

Outcome	No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
ADHD-RS	2	RCTs	no serious [a]	no serious [b]	no serious [c]	no serious [d]	no serious [e]	high
CPRS	2	RCTs	no serious	no serious	no serious	no serious	no serious	high
SNAP-18	1	RCTs	no serious	no serious	no serious	no serious	no serios	high

Abbreviations: TG. Triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

The quality of evidence is divided into 4 levels using GRADE system (high, moderate, low, very low). [a] For risk of bias, the majority of included studies were considered to be at low risk of bias. [b] Downgraded if there was a substantial unexplained heterogeneity (I^2 > 50%, P < 0.10) that was unexplained by meta-regression or subgroup analyses.[c] Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results. [d] optimal information size was not met, or the 95%CI include the null value lower and upper bounds of the 95%CI were <0.95 and >1.05, respectively. [e] Downgraded if there was an evidence of publication bias.

4. Discussion

The present meta-analysis indicates that probiotics and synbiotics may significantly improve ADHD symptoms, supporting their potential as complementary interventions. Consistent with our findings, previous systematic reviews have reported beneficial effects of probiotics in ADHD, although they did not conduct meta-analyses (40, 50).

In contrast, some prior meta-analyses found no significant therapeutic efficacy, likely due to differences in study populations and inclusion of participants with conditions other than ADHD (41, 51, 52). These discrepancies highlight the importance of considering participant characteristics, intervention type, and study quality when interpreting results.

Impairments in executive functions (i.e., cognitive flexibility, working memory, sustained attention, inhibitory control, and planning) are considered a core deficit in the cognitive function of ADHD, which may play a crucial role in the challenging adaptation of ADHD (46).

The cognitive regulation of behavior and reward perception is modulated via the norepinephrine and dopamine circuits, which connect to the prefrontal cortex and striatum, and these pathways are considered fundamental in the pathophysiology of ADHD (9). Mounting evidence suggests that the cholinergic and dopaminergic systems contribute to the pathophysiology of selective attention (53).

The gut-brain axis has emerged as a critical mechanism linking intestinal microbiota to central nervous system function, influencing mood, cognition, and behavior (54-56). In this regard, it is noteworthy that the gut is widely innervated by millions of neurons that form the enteric nervous system, which interacts with the gut microbiota (57). Additionally, the enteric nervous system, along with intestinal microbiomes, the intestinal immune system, and the endocrine system, maintains a stable intestinal microenvironment. Also, mammals exhibit reciprocal connections between the enteric nervous system and central nervous system as part of the gut-brain axis (58). Thus, it has been suggested that the brain, gut, and microbiome have bidirectional communications through the immune system, vagus nerve system, neuroendocrine system, circulatory system, and the enteric nervous system, which play a central role in normal system functionality (59). The potential mechanism of the gut-brain axis is driven by gut microbiota through interactions between immune-bacterial with the intestinal epithelial barrier, innate immune system, and neural pathways (60). A previous study revealed that changes in the gut microbiome induce the synthesis of phenylalanine, a dopamine precursor, leading to decreased neural response to reward anticipation, a hallmark of ADHD (61). Although the pathophysiology of ADHD is complex and multifactorial, microbial modulation may contribute to symptom improvement via anti-inflammatory and neurochemical pathways (62-64). Probiotics and synbiotics can restore microbial balance, reduce neuroinflammation, and regulate neurotransmitters such as dopamine, norepinephrine, serotonin, and GABA (53, 65-70). Notably, multiple-strain probiotic formulations appear to exert stronger effects than single-strain interventions, potentially due to synergistic interactions and broader modulation of gut microbiota (47-49). Finally, numerous plant-derived natural products have been identified to favorably modulate gut microbiota, potentially exerting health benefits in various diseases (71-75). Such products may hold potential relevance for future studies in the context of ADHD.

From a clinical perspective, our findings suggest that probiotic or synbiotic supplementation could serve as an adjunctive strategy in ADHD management,

particularly for patients who experience suboptimal response to standard pharmacological or behavioral therapies. Beyond symptom reduction, these interventions may improve executive functions, emotional regulation, and overall quality of life. However, heterogeneity in intervention type, dosage, treatment duration, and participant age underscores the need for personalized approaches and careful monitoring in clinical practice.

Integrating probiotics or synbiotics into ADHD care should consider a multidimensional and multidisciplinary framework, encompassing behavioral, nutritional, and psychosocial support. Preventive strategies may include modulation of gut microbiota from early childhood, dietary counseling, and targeted supplementation, especially in individuals with comorbid conditions such as metabolic or inflammatory disorders. Such translational insights can inform individualized patient management and foster interdisciplinary collaboration among clinicians, dietitians, and mental health professionals.

Despite promising results, several limitations should be acknowledged. The small number of RCTs, variability in participant age and characteristics, short treatment durations, and differences in probiotic or synbiotic strains limit the generalizability of our findings. Additionally, our meta-analysis was not registered, and some studies lacked standardized outcome measures. Future research should focus on larger, multicenter RCTs with standardized interventions and longer follow-up periods. Comparative studies evaluating single- versus multiple-strain formulations, as well as mechanistic investigations linking microbial changes to neurobehavioral outcomes, are warranted.

5. Conclusion

In summary, probiotics and synbiotics show potential as adjunctive therapies for ADHD, likely acting through immunomodulatory, microbial, and neurochemical mechanisms. While the current evidence is encouraging, further high-quality, clinically oriented studies are required to define optimal protocols, assess long-term efficacy and guide integration into multidisciplinary care frameworks.

Availability of data and material: Not applicable as no primary data was generated in this study.

Conflicts of interests: The authors have nothing to disclose.

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