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Review

Probiotics and Prebiotics in the Treatment of Autism Spectrum Disorder: A Narrative Review

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Abstract

More than half of the patients with autism spectrum disorder (ASD) have gastrointestinal (GI) comorbidities, such as constipation, indigestion, abdominal pain, and diarrhea. Recent studies suggest prescribing probiotics and prebiotics in ASD could relieve GI disturbances and behavioral issues. This narrative review generalizes the research progress on probiotic and prebiotic therapies for ASD over the past 5 years and further discusses the underlying mechanisms of interaction between probiotics and prebiotics with ASD. Preliminary evidence has demonstrated the beneficial effects of probiotics and prebiotics on GI problems, autism-related behavioral disorders, and gut microbiome composition; the mechanism of probiotics and prebiotics in the treatment of ASD is mediated through inflammatory signaling pathways, metabolic pathways, neuronal signaling pathways, and the involvement of the vagus nerve. However, the results are inconclusive and mainly generated by animal experiments. Overall, the present review recommends further standardization of clinical studies to draw more robust evidence for prescribing probiotics and prebiotics in ASD.

Keywords: autism spectrum disorder; probiotics; prebiotics; gut microbiome

1. Introduction

Autism spectrum disorder (ASD) comprises a group of neurodevelopmental disorders characterized by impairments in social communication and repetitive behaviors [1,2]. The prevalence of ASD has risen dramatically in the past 2 decades, with current incidences estimated at approximately 1.70% in children in the United States and 1.55% in Europe [3]. Data from previous systematic reviews and meta-analyses indicated that 54.8% of patients with ASD had at least 1 comorbid psychiatric disorder [4], including anxiety, depression, bipolar and mood disorders, schizophrenia spectrum, and attention-deficit/hyperactivity disorder.

Despite extensive studies, the mechanisms and etiology of ASD have not been clearly elucidated; nevertheless, it is known to be associated with genetic-environmental interactions [5]. Possible risk factors include genetic factors, a family history of psychiatric disorders, parental age, premature birth, fetal exposure to toxins, exposure of pregnant mothers to infections, and the use of psychotropic medications [2,6,7]. Data from the Global Burden of Disease Study 2019 indicate that ASD imposes enormous costs on patients' families and healthcare systems [8]; therefore, identifying more effective treatment options is crucial.

Existing treatment methods for ASD comprise both pharmacological and non-pharmacological therapies. Pharmaceuticals primarily target the comorbid symptoms of ASD [9]. Currently, mainstream drugs include serotonergic medications, atypical antipsychotics, psychostimulants, and α-2-adrenergic agonists [10,11]. These drugs regulate neurotransmitter levels and related receptor functions in the brain, often showing adverse effects (sedation, weight gain, drowsiness, and vomiting). Some over-the-counter medicationswith few adverse effects andgood tolerability are also being used in ASD [12,13], including melatonin and *N*-acetylcysteine. In addition, emerging target medications are being explored for their possible roles in ASD treatment, such as oxytocin, bumetanide, and cannabidiol [14–16], which may require more credible supporting evidence. Non-pharmacological treatments, including cognitive-behavioral therapy, probiotics and prebiotics, dietary supplements (sulforaphane, omega-3 fatty acids, and vitamin D), overall diet management (gluten- and casein-free diets), music therapy, and herbal medicine [2,9,17,18], show good tolerability and few adverse effects and have, therefore, become increasingly popular in recent years [19].

With the introduction of the concept of the brain-gut axis, the connection between the gut microbiome and the central nervous system (CNS) has become increasingly valued. The gut microbiome influences CNS activity through microbial metabolites, immune mediators, gut hormones, and the vagus nerve [20]. Gut microbiome disturbances are common in patients with ASD [21] and may result in gastrointestinal (GI) symptoms [22]. Recent reviews highlighted the importance of nutritional interventions in reducing GI symptoms by modulating the gut microbiome [20,23,24]. Oral probiotic and prebiotic management may

reduce ASD-related symptoms through the brain-gut axis. In particular, several clinical studies have revealed that probiotics and prebiotics could be promising therapies for ASD [15,25–27].

However, 2 recent systematic reviews have shown that probiotics and prebiotics had an overall limited efficacy in managing GI or behavioral problems in autism patients [28,29]. To better understand the current therapies and the rationale behind them, the present study summarized the latest clinical research on probiotics and prebiotics for ASD. In the current study, we explained the underlying mechanisms by which probiotics and prebiotics interact with ASD to intuitively demonstrate the potential of probiotics and prebiotics in ASD treatment.

2. Methods

A literature review was conducted until February 2023 using databases, including PubMed, MEDLINE, Embase, Web of Science, and Cochrane Central. The searched terms included ASD, autism, probiotics, prebiotics, therapy, gut microbiome, microbiota, brain-gut axis, and clinical trials. Additionally, sub-references of the selected articles were searched. Studies involving probiotic/prebiotic therapies and ASD, which were human clinical studies published in the last 5 years, were selected for detailed analysis.

3. The Clinical Trials of Probiotics and Prebiotics in ASD Treatment

Probiotics are living microorganisms that benefit human health by increasing short-chain fatty acids (SCFAs) production, intestinal transit regulation, and enterocyte turnover rate [30]. Some well-studied microbial species, such as *Bifidobacterium* and *Lactobacillus*, are widely used as probiotic supplements. Prebiotics, which are organic substances, have the ability to selectively promote the metabolism and proliferation of beneficial microorganisms, thereby improving host health. Some examples of prebiotics include oligosaccharides, fructans, and galactans [31]. Owing to their good tolerability and few adverse effects, probiotics and prebiotics show increasing therapeutic potential for ASD.

Clinical studies suggested that probiotic and prebiotic supplements could improve ASD symptoms and regulate gut microbiome distribution [27,32]. A longitudinal study demonstrated that after 3 months of probiotic administration, the number of *Bifidobacterium spp.* and *Lactobacillus spp.* increased in the stool of children with ASD. In addition, communication skills and social networking improved in these children, whereas childhood autism scale scores, sleep disturbances, and hyperactivity decreased [32]. Shaaban SY *et al*. [27] also reported that after 3 months of probiotic therapy, the number of *Bifidobacteria* and *Lactobacilli* increased in the stool of children with autism, whereas their body weight, autism scale scores, and GI symptoms decreased. A randomized double-blind, crossover study with placebo revealed that after 3 months of supplementation with a probiotic mixture, patients with ASD exhibited decreased GI problems and improved communication skills and maladaptive behaviors, and their parents reported reduced stress levels [33]. A crossover study revealed that colostrum (prebiotic) and *Bifidobacterium infantis* exhibited good tolerability, improved core symptoms, and decreased GI symptoms in children with ASD [34]. A study by Billeci *et al*. [35] demonstrated that after 6 months of probiotics therapy, the brain power (electroencephalography) of beta and gamma bands was modified in children with ASD. These waves (beta and gamma) are related to working-memory tasks, analytical thinking, and sensory responses [35].

Combined interventional therapies may play a unique role in reducing autism symptoms. In a previous randomized double-blind, placebo-controlled, 2-stage pilot trial, patients with ASD received probiotics or a placebo for 28 weeks, and both groups received oxytocin at week 16. The findings demonstrated reductions in autism scale scores and GI symptoms only in the group treated with the probiotic and oxytocin combination [15]. Another study demonstrated that probiotics combined with fructooligosaccharide intervention reduced autism and GI symptoms in children with ASD and modulated gut microbiome, fecal SCFAs, and plasma serotonin levels [25]. Grimaldi R *et al*. [36] focused on combined intervention and observed that exclusion diets (gluten-and casein-free diets) reduced the GI symptoms in children with ASD; however, this therapy may result in high amino acid excretion and nutrient malabsorption. When combining an exclusion diet with prebiotics, patients demonstrated a significant decrease in anti-social behavior and an increase in favorable gut microbiome [36].

In patients with autism, with or without GI symptoms, the response to probiotics may vary. A randomized double-blind, placebo-controlled trial divided children with ASD into 2 groups: one with GI symptoms (GI group) and one without GI symptoms (NGI group). Following 5 months of probiotics therapy, the NGI group exhibited improvement in core autism and GI symptoms, while the GI group exhibited improved adaptive functioning and sensory profiles compared to those of the placebo group [37]. Researchers have also reported that the plasma levels of 25(OH)D may be positively related to the response to probiotic treatment in reducing ASD severity [38].

Owing to the lack of sensitivity of the assessment tools and the limitations of small sample sizes, some studies did not report statistically significant effects. For instance, in a randomized, double-blind, placebo-controlled study [39], probiotics did not decrease Aberrant Behavior Checklist (ABC) scores in children with ASD. However, opposition/defiant behaviors, hyperactivity, and impulsivity significantly decreased. A randomized, crossover trial [40] indicated that after 8 weeks of therapy, the quality of life and emotional stability improved from baseline in chil-

dren with ASD, but the differences between the probiotic and placebo effects were not statistically significant.

A summary of clinical studies on probiotics/prebiotics for ASD over the last 5 years is presented in Table 1 (Ref. [15,25,27,32–37,39,40]). Although probiotics and prebiotics used in the trials differed in their forms, dosages, and microbiota composition, all these studies demonstrated their benefits in improving ASD-related behavioral problems and GI symptoms. However, owing to the heterogeneity among the trials, identifying the particular strain or therapy that exerts the greatest efficacy in decreasing ASD symptoms is challenging.

4. The Mechanism Underlying Probiotics and Prebiotics Interactions in ASD

4.1 GI Symptoms and Unique Composition of Gut Microbiome in ASD Patients

GI symptoms (i.e., smelly stools, constipation, diarrhea, gas, and vomiting) were about 4 times more common in children with ASD than in healthy individuals [41]. Some studies have demonstrated that GI disorders may correlate with autism severity,indicating that patients with GI problems have higher autistic scores than those without them [42,43]. The high prevalence of GI disturbances has driven researchers to highlight the relationship between the gut microbiome and ASD. Further studies have identified differences in the distribution of the gut microbiome between patients with ASD and healthy individuals. In a study by Iglesias-Vázquez *et al*. [44], children with ASD exhibited a greater abundance of *Bacteroides*, *Parabacteroides*, *Clostridium*, *Faecalibacterium,* and *Phascolarctobacterium* at the genus level and a decreased level of *Coprococcus* and *Bifidobacterium,* compared to neurotypically developed children. However, Andreo-Martínez *et al*. [45] came to a different conclusionand observed that only *Streptococcus* and *Bifidobacterium* were decreased in ASDpatients than in healthy individuals. Furthermore, no consistent conclusions have been reached regarding the abundance of phyla, such as *Bacteroidetes*, *Firmicutes,* and *Actinobacteria*, with no firm conclusions regarding whether ASD individuals show high or low abundance [46–48]. In addition, a dysregulated microbiome composition may negatively affect GI functions. Dan *et al*. [49] reported an increased α-diversity in ASD patients with chronic constipation; however, this was not discovered in those without constipation. GI disorders may not be directly attributed to ASD but rather alterations in metabolites that are closely related to the gut microbiome, such as acetate, propionate, and valerate, which have been linked to gut microbiome composition [41].

4.2 Gut Microbiome and ASD

Growing evidence has indicated that metabolites generated by the gut microbiome, also known as neuroactive microbial metabolites and molecules, can pass through the blood-brain barrier and directly regulate neural networks, thereby influencing affection and social and cognitive functions [50]. One of these metabolites, 4-ethylphenyl sulfate (4EPS), has recently gained traction. Needham *et al*. [51] observed that the plasma levels of 4EPS increased 6.9-foldin patients with ASD. An animal study [52] demonstrated that 4EPS enters the brain and affects oligodendrocyte function and myelin patterning, thus inducing anxiety-like behavior in mice. However, the specific mechanisms by which 4EPS exerts these effects and how changes in myelination affect behavior remain unknown. Moreover, the levels of SCFAs, another gut-derived metabolite, were significantly altered, exhibiting lower levels in patients with ASD and other neurological disorders [53]. Previous studies have indicated that SCFAs crossing the CNS retain neuro activity [54,55]. In animal models, SCFAs promote microglial maturation, modulate neurotransmitters and neurotrophic factors, and increase histone acetylation [56,57]. In human studies, SCFAs testing predominantly relies on stool samples (instead of colon samples), which raises the potential for different biases caused by intestinal transport, permeability, and sample handling.

The gut microbiome can directly produce neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT), γ-aminobutyric acid (GABA), and glutamate, which influence the enteric nervous system (ENS) and CNS activity [58]. In total, 90% to 95% of serotonin is found in the GI tract(mainly stored in enterochromaffin cells), indicating that serotonin is a key signal in brain-gut interactions [59]. The gut microbiome is also involved in the production of intestinal 5-HT [60]. Germ-free animal studies have indicated that microbes might modulate the secretion of 5-HT [61] and the development and/or function of enterochromaffin cells [62]. In addition, the gut microbiome may modulate 5-HT transporter and/or 5-HT receptor expression, thereby exerting a regulatory effect on 5-HT homeostasis [63]. In contrast, GABA and glutamate, the main excitatory and inhibitory neurotransmitters in the CNS, control the excitatory/inhibitory balance and play key roles in the pathogenesis of ASD [64]. The microbiome may influence the circulating levels of GABA. For instance, germ-free mice exhibit lower levels of GABA in the stool and blood than colonized mice [65]. Similarly, antibiotics can modify fecal GABA levels in model mice [66]. The gut microbiome may also indirectly affect glutamatergic pathways by regulating tryptophan metabolism, which contributes to the synthesis of neuroactive microbial molecules [60].

Previous studies have identified neuroimmune disturbances in ASD, including increased astrocyte and microglial activity. The mucosal immune system, an extensive immune system of the intestine, is chronically exposed to microorganisms and metabolites. Some microbiome products, such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), cross the mucosal immune system and activate inflammatory cytokines [67]. Conversely, blood-

Table 1. Summary of clinical trials investigating probiotic and prebiotic supplements for ASD in the last 5 years.

Participant (age)	Trail design (sample size)	Interventions	Dose and duration	Key findings	Ref
Children with ASD (18–72 months)	A randomized, double-blind, placebo-controlled study (63)	*Streptococcus thermophilus*; *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*; *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus para-casei*, *Lactobacillus delbrueckii subsp*.	6 months	Decreased frontopolar power, with an increase in frontopolar coherence in beta and gamma bands in electroencephalography.	Billeci *et al*. 2023 [35]
Children with ASD (2–5 years)	Before-after study in the same patients (40)	*Bifidobacterium spp.*; *Lactobacillus spp.*; casein-free whey powder; minced cooked yellow vegetables.	3 months	↑*Bifidobacterium spp.* and *Lactobacillus spp.* in the stool; ↓weight and BMI; improved autism scale (CARS), sleep disturbances, communication, and social networking; reduced hyperactivity.	Meguid *et al*. 2022 [32]
ASD patients (24 months–16 years)	a randomized double-blind crossover study with placebo (61)	*Limosilactobacillus fermentum LF10*; *Ligilactobacillussalivarius LS03*; *Lactiplantibacillus plantarum LP01*; *Bifidobacterium longum DLBL*.	10×10^9 CFU/AFU per day for 3 months	Improved GI symptoms, communication skills, maladaptive behaviors, and perceived parental stress level.	Guidetti *et al*. 2022 [33]
ASD patients (3–20 years)	A randomized, double-blinded, placebo-controlled, 2-stage pilot trial (35)	*Lactobacillus plantarum PS128*; Oxytocin.	6×10^{10} CFU per capsule, 2 capsules per day for 24 weeks	Improved autism scale (ABC and SRS) and GI symptoms; ↑favorable gut microbiome hubs and numbers of connection edges.	Kong *et al*. 2021 [15]
Children with ASD (3–9 years)	A double-blind, placebo-controlled study (26)	*Bifidobacterium infantisBi-26*, *Lactobacillus rhamnosusHN001*, *Bifidobacterium lactisBL-04*, *Lactobacillus paracaseiLPC-37*; fructooligosaccharide.	10^{10} CFU per day for 30–108 days	↑*Bifidobacteriales* and *B. longum*; ↓*Clostridium*; ↑fecal SCFAs; ↓plasma serotonin; ↑homovanillic acid; improved autism scale (ATEC) and GI symptoms.	Wang *et al*. 2020 [25]
Children with ASD (18–72 months)	A randomized, double-blind, placebo-controlled trial (85)	*Streptococcus thermophilus*; *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*; *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus para-casei*, *Lactobacillus delbrueckii subsp*.	Each packet contained 450 billion of probiotic strains; 2 packets per day in the first month, 1 packet in the following 5 months	Improved GI symptoms, adaptive functioning, and sensory profiles in ASD children with GI symptoms; improved autism scale (ADOS-CSS) in ASD children without GI symptoms.	Santocchi *et al*. 2020 [37]
Children with ASD (2–11 years)	A randomized, double-blind, cross-over study (8)	*Bifidobacterium infantis*; colostrum.	20 billion CFU per day for 4 weeks	Reduced aberrant behaviors and GI symptoms; ↓intracellular expression of certain cytokines (CD4+ and CD8+ T cells).	Sanctuary *et al*. 2019 [34]
Boys with ASD (7–15 years)	A randomized, double-blind, placebo-controlled study (71)	*Lactobacillus plantarum PS128*.	4 weeks	Reduced opposition/defiance behaviors and hyperactivity, and impulsivity.	Liu *et al*. 2019 [39]

Table 1. Continued.

Participant (age)	Trail design (sample size)	Interventions	Dose and duration	Key findings	Ref
Children with ASD (3–12 years)	A randomized, crossover trial (13)	*Lactobacilli*; *Bifidobacteria*; *S. Thermophiles*.	900 billion bacteria per packet, a half packet twice daily for the first 4 weeks, then increasing to an entire packet twice daily for the last 4 weeks	Improved quality of life and emotional stability.	Arnold *et al*. 2019 [40]
Children with ASD (5–9 years)	Before-after study in the same patient (30)	*Lactobacillus acidophilus*; *Lactobacillus rhamnosus*; *Bifidobacterialongum*.	100×10^6 per day for 3 months	↑*Bifidobacteria* and *Lactobacilli* in the stool; ↓body weight; improved autism scale (ATEC) and GI symptoms.	Shaaban *et al*. 2018 [27]
Children with ASD (4–11 years)	A randomized, double-blind, placebo-controlled study (26)	B-GOS® (a galactooligosaccharide)	6 weeks	Improvements in anti-social behavior; ↑*Lachnospiraceae* family.	Grimaldi *et al*. 2018 [36]

↑: increase, ↓: decrease.

ASD, autism spectrum disorder; GI, gastrointestinal; ADOS-CSS, Autism Diagnostic Observation Schedule - Calibrated Severity Score; ATEC, Autism Treatment Evaluation Checklist; CARS, Childhood Autism Rating Scale; SCFAs, short-chain fatty acids; SRS, Social Responsiveness Scale; BMI, body mass index; CFU, colony-forming unit; AFU, active fluorescent unit; ABC, Aberrant Behavior Checklist.

borne cytokines and chemokines can cross the blood-brain barrier and influence cognitive function and behavior in ASD patients [68]. Microbial metabolites(such as SCFAs) can regulate tight junction proteins, increase intestinal barrier function, and hinder inflammatory reactions in patients with ASD [69]. In conclusion, treatment with probiotics combined with colostrum leads to a reduction in intracellular cytokine expression by $CD4^+$ and $CD8^+$ T cells [34]. In animal studies, germ-free mice exhibit immature and deformed microglia [56], suggesting that microglial maturation may be associated with the gut microbiome. Therefore, neurons and microglia can be directly influenced by the microbiome as well as their metabolites and indirectly affected by inflammatory cytokines, which are also controlled by the gut microbiome [70].

This evidence highlights the importance of microbiome balance and the promising role of probiotics and prebiotics in ASD management.

4.3 Probiotics/Prebiotics Treat ASD by Regulating the Gut Microbiome

Probiotics have been shown to readjust the abundance of the gut microbiome [32,71], supporting their involvement in reducing GI symptoms and cognitive and behavioral problems. In a study of Dip2a knockout mice [72], an animal model of ASD, researchers observed an increased abundance of beneficial bacteria, such as *Dubosiella* and *Bifidobacterium*, following probiotic supplementation. In contrast, the number of harmful bacteria such as *Lachnospiraceae NK4A136 group*, *Alistipes*, and *Enterorhabdus* decreased. Similarly, in a human study [25], the administration of probiotics combined with prebiotics in children with ASD resulted in an increased number of *Bifidobacteriales* and *B. longum* (beneficial bacteria) and decreased number of *Clostridium* (suspected pathogenic bacteria). With the growing recognition of the gut microbiome's role in treating ASD and related GI problems, therapies that rectify gut microbiome and its correlation with the host have been increasingly valued. The possible mechanisms by which probiotics/prebiotics interact with ASD include inflammatory signaling pathways, metabolic pathways, neuronal signaling pathways, and the involvement of the vagus nerve, as shown in Fig. 1.

Probiotics are widely recognized for their therapeutic mechanisms in the stabilization of the intestinal barrier and downregulation of inflammatory states [73]. Certain strains, such as *Lactobacillus*, may regulate cytokine production, while *Bifidobacterium* may induce tolerance acquisition [74]. Oral probiotic administration to pregnant mice has been shown to downregulate IL-6 and IL-17a levels in the maternal serum and fetal brain, thereby decreasing the risk of ASD in offspring [75]. Furthermore, probiotics and prebiotics have been shown to modulate neurotransmitter levels. In the same study, probiotics decreased GABA levels in the prefrontal cortex of offspring mice and improved ASD-like behaviors. In another study, *Bifidobacteria* and *Lactobacilli* supplementation relieved the glutamate excitotoxic effects induced by propionic acid and clindamycin while exacerbating the depletion of GABA and Mg^{2+} [76]. These results are consistent with those reported by Lin *et al*. [77], who observed that oral probiotics decreased glutamate receptor signaling in the hippocampus of the mice offspring in an ASD-like model.

Furthermore, probiotics can function through their metabolites, such as SCFAs, phenolic compounds, and free amino acids. It inhibits the nuclear factor kappa-B (NF-κB) pathway, Treg cell expression, and pro-inflammatory cytokine production by binding to specific receptors on intestinal epithelial cells [78]. Animal and human studies on ASD have demonstrated increased production of beneficial SCFAs (such as butyric acid) following probiotic/prebiotic supplementation [25,79]. In addition, microbes indirectly intervene with neurotransmitter production by affecting circulating amino acid levels [80]. For instance, *Bifidobacterium infantis* increases the levels of tryptophan, a 5-HT precursor [81]. Therefore, a targeted increase or decrease in the abundance of this precursor-producing microbiome could modulate monoamine neurotransmitters in the brain, indicating it as a potential treatment option for ASD.

In particular, the vagus nerve plays an important role in the bi-directional interaction between the gut microbiome and the brain, allowing for transmitting information and responding to changes in the gut microbiome. Enteroendocrine cells communicate with the vagus nerve through neuropods, thus allowing rapid neurotransmission [82]. Therefore, the effects of probiotics and prebiotics on neurotransmitter levels may be partially mediated by the vagus nerve. In addition, gut peptide hormones derived from GI endocrine cells exhibit a variety of physiological functions, many of which activate their receptors in the vagus afferent neurons and brain, involved in the regulation of neural functions [83]. Indeed, elevated levels of secretin and decreased cholecystokinin were observed in germ-free mice [84]. Thus, gut peptide hormones may modulate brain-gut axis signaling and could be related to the therapeutic mechanism of probiotics and prebiotics.

5. Discussion

The bi-directional crosstalk between the gut microbiome and the brain, also termed the microbiome-gut-brain axis, is widely recognized. Interventions that modulate the gut microbiome may improve CNS disorders via this axis. In recent years, probiotics and prebiotics, which have good tolerability and few side effects, have gradually gained traction in the treatment of various neurodevelopmental disorders.

The clinical evidence presented in this review suggests that prebiotic or probiotic supplementation decreases GI symptoms and/or ASD-related behaviors in patients with ASD. Most of these studies focused on children, while

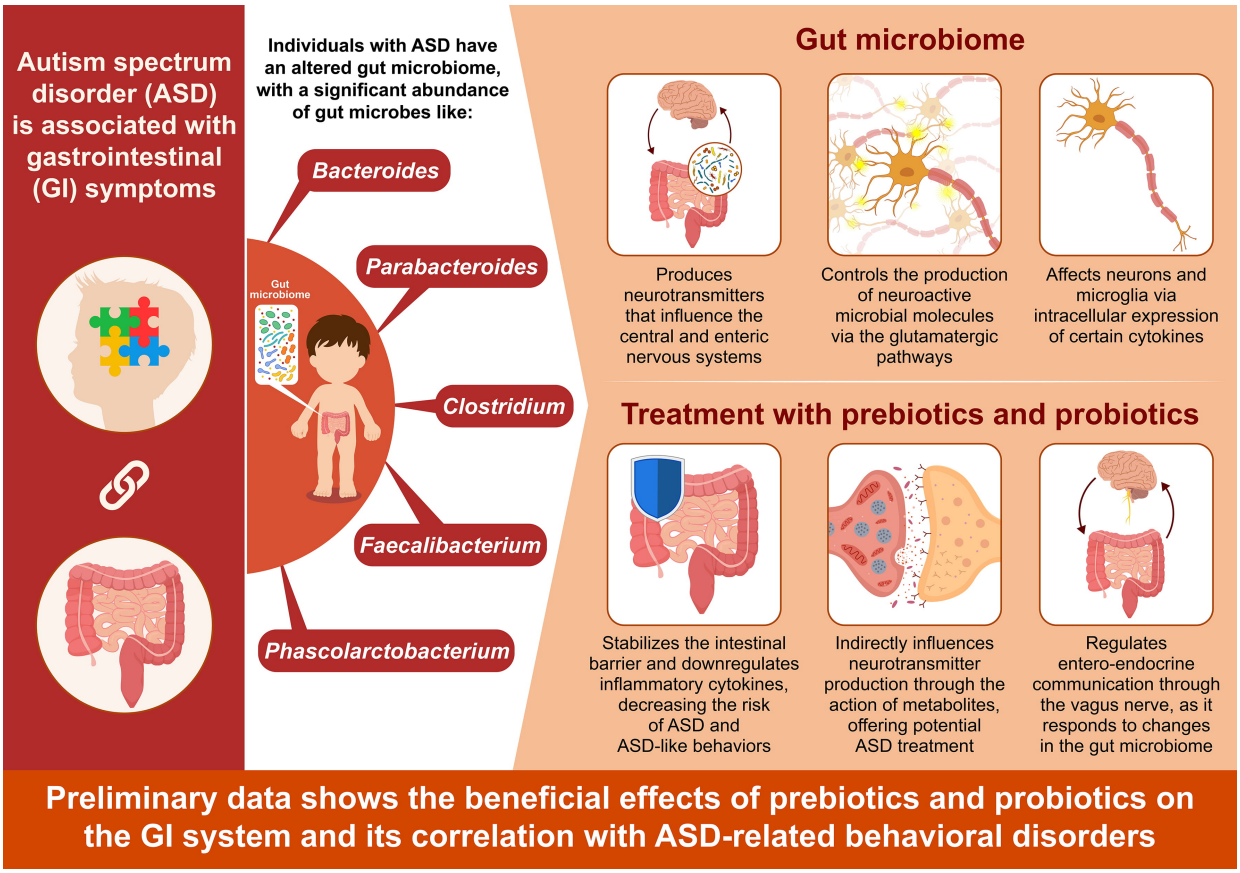

Fig. 1. The possible mechanisms by which probiotics/prebiotics interact withautism spectrum disorder (ASD).

one study examined both children and adults [15]. *Bifidobacterium* and *Lactobacillus* were the most common species found in the probiotic products, followed by *Streptococcus thermophilus*. In these studies, probiotics and prebiotics were typically administered for 4 weeks to 6 months. Among the previously-performed randomized, double-blind, placebo-controlled trials, a trial by Guidetti [33] demonstrated that probiotics decreased GI symptoms, behavioral disorders, and parenting stress levels. These results are consistent with Santocchi's study [37], which demonstrated a decrease in ASD severity and adaptive function. Wang *et al*. [25] reported the beneficial effects of probiotics combined with prebiotics (fructooligosaccharide) on gut microbiome composition, hyper-serotonergic state, and dopamine metabolism problems in ASD patients. In addition, Arnold *et al*. [40] reported no serious adverse events in probiotic therapy for ASD. However, the improvement of the main outcomes (quality of life and anxiety) has not reached statistical significance. The heterogeneity across studies makes it challenging to draw conclusions, and more human studies on probiotics and prebiotics therapies with consistent inclusion and evaluation criteria are required to clarify the future of these treatments. Moreover, most studies have focused on immediate or short-term efficacy and lacked follow-up data for long-term benefits. The variation in species, dosages, and durations of probiotics/prebiotics in these studies suggest the significance of individualized treatment, considering the specific characteristics of ASD and gut microbiome composition [85]. Currently, probiotics have been considered safe for consumption in food and dairy products, but some researchers believe that probiotics may increase the risk of infection in chemotherapy patients [86]. Therefore, systematic reviews on the safety and adverse events associated with probiotic and prebiotic therapies are necessary.

Current evidence suggests that the immune system, microbial metabolites, neurotransmitters, and vagal system mediate the brain-gut communication. Abnormalities in microbiome composition and/or its interactions with the host may lead to GI problems as well as a risk of brain dysfunction through the microbiome-gut-brain axis [87]. Probiotics and prebiotics regulate the function of the microbiome-gut-brain axis by modulating the gut microbiome. This review provided preliminary evidence that probiotic/prebiotic management can downregulate the inflammatory state, as their associated beneficial metabolites stabilize the intestinal barrier, thereby decreasing immune disturbances in ASD. In addition, they can modulate brain activity by directly or indirectly affecting the level of neurotransmitters and the development of microglia and astrocytes. As previously mentioned, the gut microbiome is involved in 5-HT synthesis, transport, and metabolism, and

dysfunction in the 5-HT system has been implicated in the development of ASD. This finding is supported by the identification of serotonin transporter and tryptophan hydroxylase 2 gene polymorphisms in ASD patients [88]. However, more direct evidence is needed to clarify how the microbiome influences autism pathology through the serotonin pathway. Furthermore, the available evidence has some limitations. For instance, the effects of oral probiotics/prebiotics on intestinal microbial homeostasis may be short-lived [89], and achieving long-term results through probiotic therapy remains unknown. Furthermore,many studies examining the effects of probiotics and prebiotics on ASD have been conducted using animal models, and the complexity of gut microbiome and variations across species limits the applicability of animal-study findings to humans. Additionally, the bi-directional effect of the brain-gut axis makes it difficult to discern the origin of this problem. The microbiome may also be affected by ASD [29].

6. Conclusions

Probiotic and prebiotic supplementation may show beneficial effects on ASD, but the heterogeneity across studies makes it challenging to draw conclusions. Although gut microbial dysbiosis is associated with ASD pathogenesis, current knowledge is insufficient to elucidate the interaction between the microbiome and the host and to investigate how their metabolites influence intestinal homeostasis. Regarding microbiome alterations in ASD, which microorganisms are abnormal and whether a single microbe or colony can be identified as a culprit remain unclear.

Author Contributions

FF and SZ designed the research study. QW collected the references and FH provided help and advice on the table and figures. SZ and FF wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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