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IUPHAR review: Targeted therapies of signaling pathways based on the gut microbiome in autism spectrum disorders: Mechanistic and therapeutic applications

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ABSTRACT

Autism spectrum disorders (ASD) are complex neurodevelopmental disorders characterized by impairments in social interaction, communication and repetitive activities. Gut microbiota significantly influences behavior and neurodevelopment by regulating the gut-brain axis. This review explores gut microbiota-influenced treatments for ASD, focusing on their therapeutic applications and mechanistic insights. In addition, this review discusses the interactions between gut microbiota and the immune, metabolic and neuroendocrine systems, focusing on crucial microbial metabolites including short-chain fatty acids (SCFAs) and several neurotransmitters. Furthermore, the review explores various therapy methods including fecal microbiota transplantation, dietary modifications, probiotics and prebiotics and evaluates their safety and efficacy in reducing ASD symptoms. The discussion shows the potential of customized microbiome-based therapeutics and the integration of multi-omics methods to understand the underlying mechanisms. Moreover, the review explores the intricate relationship between gut microbiota and ASD, aiming to develop innovative therapies that utilize the gut microbiome to improve the clinical outcomes of ASD patients. Microbial metabolites such as neurotransmitter precursors, tryptophan metabolites and SCFAs affect brain development and behavior. Symptoms of ASD are linked to changes in these metabolites. Dysbiosis in the gut microbiome may impact neuroinflammatory processes linked to autism, negatively affecting immune signaling pathways. Research indicates that probiotics and prebiotics can improve gut microbiota and alleviate symptoms in ASD patients. Fecal microbiota transplantation may also improve behavioral symptoms and restore gut microbiota balance. The review emphasizes the need for further research on gut microbiota modification as a potential therapeutic approach for ASD, highlighting its potential in clinical settings.

1. Introduction

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental disorder with a robust hereditary foundation. ASD is characterized by stereotyped, repetitive behavior and poor social and communication abilities. ASD has a substantial impact on society and the progress of children. The overall prevalence of ASD in 8-year-old children was 16.8 per 1000 in 2014; the rate was notably more significant in males (26.6 per 1000) than in females (6.6 per 1000) [1]. Currently, it costs £ 0.92 million in the United Kingdom (UK) and $1.4 million in the United States (US) to support a child with ASD without intellectual disabilities. ASD children have particular schooling and

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treatment needs and their parents are impacted due to the additional burden [2]. An estimated 52 million people were predicted to have an ASD in 2010, which translates to a prevalence of 7.6 per 1000 or one in 132 people. There was no conclusive proof of a shift in the frequency of ASDs between 1990 and 2010, even after considering methodological differences. There was minimal regional heterogeneity in the frequency of ASDs worldwide [3].

Researchers have identified hundreds of genes that are associated with high levels of autism risk. New neuroscience methodologies are enhancing the understanding of the underlying causes of ASD. New data indicates that signal transduction molecular processes influence pathogenic processes, allowing for the accurate identification of molecular targets and innovative approaches. This review discusses novel treatment modalities for ASD, neuroscience technology and signal transduction molecular events. CRISPR-Cas9, a gene-editing technique, has shown positive results in ASD-related fragile X syndrome models [4]. Signal transduction molecular events, which involve pathways related to transcription, translation, synaptic transmission, epigenetics and immunoinflammatory responses, help scientists to identify molecular targets for personalized treatments. Novel therapeutic approaches such as gene substitution, editing and translating oligonucleotides, aim to reduce the adverse effects of mutations by modifying gene expression [5]. The gut microbiota composition can affect brain function, leading to diarrhea and constipation. Children with ASD often have a less diverse gut microbiota with altered bacterial populations [6]. Fecal microbiota transplantation or probiotics may ameliorate the symptoms of ASD. Multiplying gut microbiota may be a functional therapeutic approach [7]. A comprehensive study reveals a strong correlation between ASD and genetic and environmental factors with elevated reactive oxygen species (ROS) causing 4-hydroxyphenylacetic acid (HPHPA), oxidative stress (OS) and redox imbalance [8]. Early detection and management of antioxidant status can improve long-term prognosis and prevent irreparable brain damage in individuals with ASD, which is also associated with dysbiosis [9]. Antibiotic use, delivery methods and early colonization can affect the link between intestinal microorganisms, autism and gastrointestinal diseases. Short-chain fatty acids (SCFAs) produced by plant-based fiber fermentation can impact the gastrointestinal and neurological development of autistic patients [10].

The microbiome pertains to the collective of bacteria and their genes. The human gut microbiota contains approximately 150 times more genes than the entire genome. The human body contains more than 100 trillion microorganisms that contribute to various biological processes including maintaining health (Fig. 1) [11]. The gut microbiota plays an important role in regulating metabolism, barrier homeostasis, inflammation and hematopoiesis [12]. The host-microorganism relationship is a crucial factor in both health and disease. Host characteristics such as age, environment, nutrition and lifestyle significantly influence the diversity of gut microbiota. Nutrition is considered one of the primary variables that can affect the function of gut microbiota [13]. Recent research suggests that neurotransmitters including serotonin and dopamine, which are endogenous markers, play a significant role in the pathogenesis and development of ASD [14]. This review links gut microbiome imbalances to ASD, demonstrating dysbiosis disrupts gut-brain communication, affects neurological development and suggests probiotics, prebiotics and dietary changes can significantly improve outcomes.

2. Microbiota–gut–brain axis

The CNS regulates gut function, which may affect nerve cells and the gastrointestinal tract. Gut flora may influence nervous system disorders and control the gastrointestinal tract. The microbiota-gut-brain axis is influenced by the intricate interaction between gut microorganisms and the host (Fig. 2). Studies have found a significant connection between gut microbiota and neurological function, with evidence suggesting four levels of neural control in the gastrointestinal tract: autonomic nervous system, enteric nervous system (ENS) and CNS [15,16]. The ENS regulates the gastrointestinal tract and CNS, connecting motor and sensory

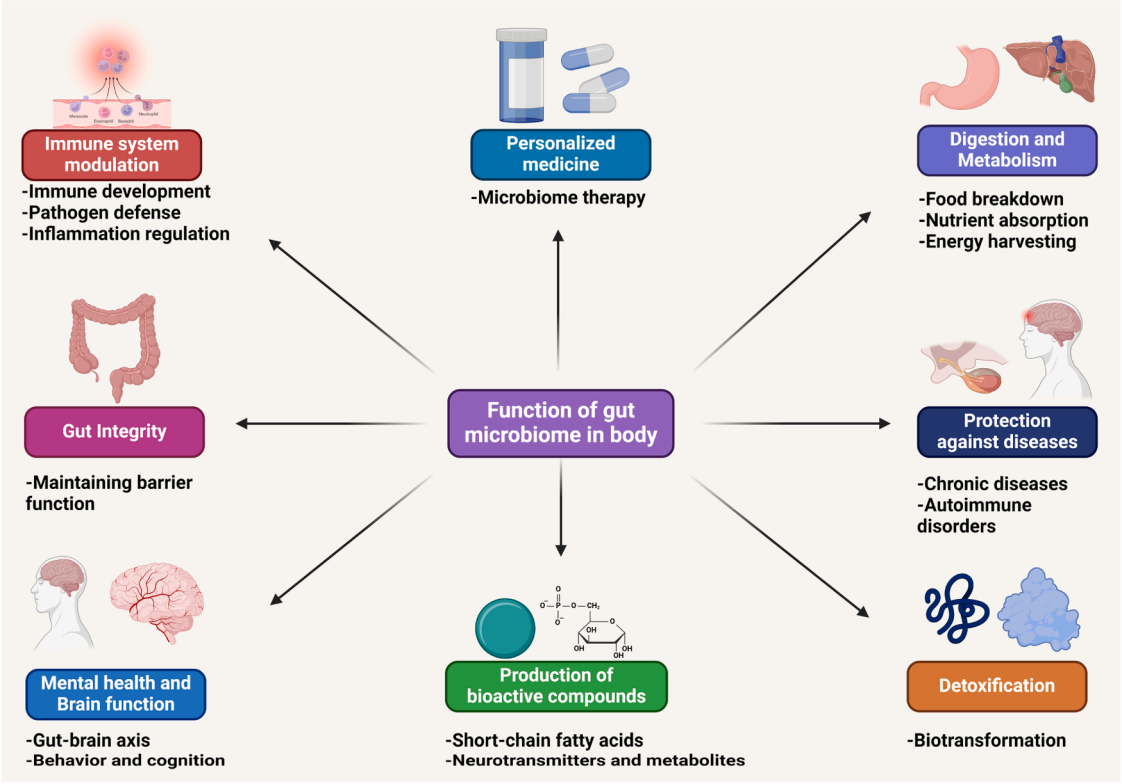

Fig. 1. Illustration of the fundamental roles and functions of the gut microbiome in the human body.

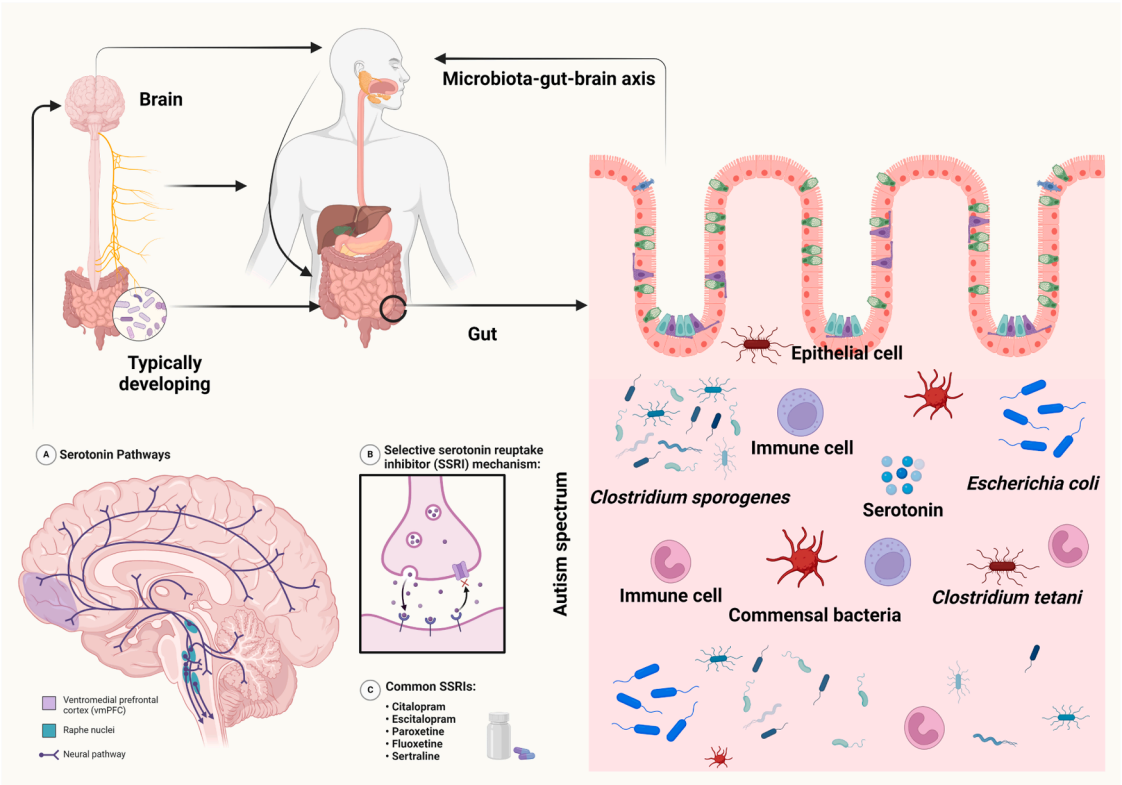

Fig. 2. Illustration of the role and link among the microbiota, gut and brain.

neurons. The ENS forms the foundation for the microbiota-gut-brain axis activity through the neuroendocrine network [17]. The vagus nerve regulates the function of various organs, heart rate and intestine motility and can send immune messages to the CNS. The vagus nerve can also trigger anti-inflammatory reactions and regulate the functions of the brain [18]. Another study found that animals treated with probiotics and bifidobacteria showed no significant behavioral changes even after vagotomy [19]. Microorganisms can alter host neurophysiological function by attaching to receptors inside and outside the stomach, as demonstrated in mice with *L. rhamnosus* probiotics [18]. The gut microbes in the large intestine break down food fibers to produce SCFAs. SCFAs may enhance neurodevelopment and cognitive performance in neurodegenerative diseases in animal models [20]. A study showed that the injection of propionic acid by Macfabe into rats resulted in neurochemical alterations and the development of autism-related characteristics [21]. Neurochemical changes including neuroinflammation, OS and antioxidant depletion, induce mitochondrial dysfunction, while microbiota-generated chemicals such as melatonin, histamine, acetylcholine, serotonin and acetylcholine regulate the gut-brain axis [22]. The gut microbiota may exacerbate autism, a non-immune condition, with physiological parameters including autoimmune reactions and food reactions strongly associated with the gut microbiome [23]. Currently, no proven therapy exists for the primary symptoms of ASD, but adjusting the function of microbiota and the microbiota-gut-brain axis may lead to novel therapeutic approaches [24]. Microbes possess more genes than humans (1.3 and 100 per cell) [25]. Human genetics, immunological reactions, nutrition, antibiotics, livelihood and location impair the functions of the microbiome. Location in the microbiome refers to the geographical and environmental factors that influence the composition and diversity of microbial communities in the human body [26]. The microbiota-gut-brain axis is a crucial communication link between the gut bacteria and the central nervous system (CNS), regulating neuroinflammation, neurotransmission, stress activation, blood-brain barrier (BBB) formation, myelination, neurogenesis and complex brain behaviors [27,28]. The microbiota-gut-brain axis controls the functions in the brain such as neurotransmitter synthesis and behavior regulation through a communication channel between gut microbes and the CNS. The gut microbiota is linked to social impairment and repetitive behavior in individuals with ASD. ASD is associated with altered immune responses and gut microbiota differences from developed individuals [29]. Animal models show changes in microbiota composition that affect neurological and behavioral outcomes. The microbiota is essential in interventions including fecal microbiota transplant therapy [30]. Several factors influence ASD including gut-brain-microbiota axis dysbiosis, which can affect immune responses, microbial metabolites and gut permeability. Current treatments include fecal microbiota transplantation, microbiota transfer treatment, nutritional supplements, prebiotics and probiotics [31]. Previous studies found that single nucleotide variants (SNVs) were associated with ASD in 26 youngsters, enriching genes related to retrograde axonal transport, protein glycosylation and immune response and correlated with microorganisms and neurotransmitter metabolic network [32]. ASD is associated with alterations in gut microbiota and the immune system, which may affect the development of the brain. Early childhood probiotics could improve therapies and prevent ASD in women, potentially guiding preventative measures [33].

3. Autism and gut microbiome

A study [34] showed the possible impact of prebiotics and probiotics on the gut microbiome and its effects on behavioral symptoms of ASD. Probiotics ameliorate behavioral symptoms of ASD. The imbalance in the gut microbiota can promote intestinal permeability, leading to gastrointestinal symptoms and systemic inflammation [34]. Helena et al. have reported that the most common characteristics of people with autism are their peculiar approaches to learning, paying attention, and responding to various sensations [35]. Autism is typically believed to be a psychiatric disorder that avoids gastrointestinal symptoms. Studies

have shown that gastrointestinal discomfort is usually associated with autism [36] and is thought to be correlated with the degree of autism [37]. Multiple independent investigations confirm the GI dysfunctions in these children including flatulence, bloating, diarrhea, constipation and ill-formed feces [38,39].

Children with autism may experience intestinal permeability and potential neurological impairment due to the absorption of neurotoxic chemicals through an inflamed gut barrier [40]. Accumulating studies have indicated that ASD is associated with gut microbiota, but it remains unclear whether abnormal eating and nutrition habits are directly responsible for the development of ASD [41,42]. Finegold et al. found autistic children may have intestinal dysbiosis, a chronic imbalance of gut microbiota, which has been found in numerous autistic patients (Table 1) [43]. The immune system weakens when harmful microbes are present, populations grow and uncommon bacteria may induce autism in children [44]. Studies have revealed that the microbiome of newborns improves when exposed to new dietary regimens and life experiences, assisting digestion and promoting host health by breaking down plant polysaccharides [45]. Parracho et al. suggest that autistic children may have intestinal mucosal dysbiosis and abnormal carbohydrate digestion with fewer Bacteroidetes, Firmicutes, and Betaproteobacteria [35]. Significant differences were found in the gut microbiome of children with autism including a higher incidence of *Bacteroides vulgatus* and *Desulfovibrio* species in their stools compared to the healthy controls [43]. *Clostridium* and *Ruminococcus* species in late-onset autism children significantly differ from the normal children, as evidenced by anaerobic culturing techniques and PCR targeting 16S rDNA [43]. In addition, a study using fluorescence *in situ* hybridization found that children with ASD have higher levels of *Clostridium hystolyticum* than the average [35]. Furthermore, Sandler et al. found that over-colonization of neurotoxin-producing bacteria in the gut microbiota may exacerbate autism symptoms with *Clostridium tetani* being a potential pathogen [46]. Since Clostridium can form propionate [47] and propionate has been demonstrated to induce neurological damage in rats [48], there is a notion that the prevalence of autism is correlated with prolonged exposure to *Clostridium* spores. A study found that autistic children had significantly higher *Lactobacillus levels* and lower Enterococcus and Bifidobacterium levels [49]. Furthermore, Adams et al. showed increased *Lactobacillus* strain levels in autistic patients, with reduced levels of *Klebsiella oxytoca* and *Bacillus* spp., suggesting a connection between ASD and gut microbiota [36]. Kang and co-workers found unique gut bacteria associated with ASD including adaptable Prevotella, Coprococcus and unidentified Veillonellacea [50].

The microbiota composition of ASD patients may affect microbial interactions, reducing diversity and function, while high Prevotella levels are associated with untreated HIV infection [51]. The production of bacterial metabolites can affect the function of the brain with autism patients being susceptible to bacterial metabolites. Elevated HPHPA excretion causes catecholamine depletion, worsening autistic symptoms in experimental animals [44]. Autism rates are higher in individuals with high levels of Clostridium, Sarcina, Caloramator genera, Alistipes and Akkermansia species in their microbiota with significant differences in volatile organic compounds and free amino acids [52]. Kang co-workers using 16 s rRNA gene pyrosequencing analysis from fecal DNA samples showed reduced amounts of Prevotella, Coprococcus, and unclassified Veillonellaceae in autistic children [50]. Additionally, Colorado and Arizona found a correlation between ASD and gut microbiome composition, inappropriate speech decline, and social withdrawal in individuals with ASD [53].

Table 1
The table shows the impact of various microbes on autistic patients.

Microbes	Microbial range in patients with autistic	Effects on patients	Ref.
Blautia	Reduced	Bacteria involved in bile acid production, the precursor to serotonin and tryptophan, affect brain serotonin levels and are linked to autism behavior.	[54]
Clostridium	Enhanced	The production of propionate and endotoxins may be linked to the severity of symptoms of ASD.	[43, 55]
Candida albicans	Enhanced	The release of ammonia and absorption of carbohydrates may lead to an excess of GABA production, potentially causing autistic behavior.	[56]
Prevotella	Reduced	Autism is believed to result in poorer carbohydrate metabolism due to the involvement of genes involved in saccharide metabolism.	[50]
Proteobacteria	Enhanced	The substance decreased GSH levels and inflammation and produced lipopolysaccharide, the primary cause of immunological dysregulation in autism.	[57, 58]
Bifidobacterium	Reduced	Autism-related children have reduced GABA levels due to the loss of GABA synthesis by bifidobacterium.	[59]
Faecalibacterium prausnitzii	Enhanced	The process produces butyrate, an anti-inflammatory substance that is believed to be beneficial for children with autism.	[60]
Bacteroides	Enhanced	The production of short-chain fatty acids, particularly propionic acid, may impact autistic behavior via the gut-brain axis.	[61]

4. Animal model gut microbiome on endophenotypes associated with ASD

Gastrointestinal and neurobehavioral symptoms in children with ASD may be associated with changes in the intestinal microbiota composition. Gut dysbiosis in ASD is a common disease (Table 2) [62]. Studies have found that gut microbiota produces co-factors and vitamins and induces the development of autism [63,64]. A rat without germs shows less social exploration of a new mate [65]. The amygdala, a crucial emotional brain region, has been found to exhibit altered gene expression, exon use and RNA editing [66]. Clarke et al. reported that male mice showed more social behavioral impairments, which is consistent with the ASD trait of male bias [67]. The FDA-approved medication risperidone has been discovered not to improve social impairments in animal models of ASD [68,69]. The neurodevelopmental roots of ASD can be significantly affected by the maternal environment (Fig. 3).

Heijtz et al. have revealed that the expression of PSD-95 and synaptophysin in the striatum is associated with behavioral changes [70]. Previous studies have confirmed that the behavioral alterations observed in mice treated with antibiotics and those without germs can be linked to learning and memory deficiencies [71,72]. Animals without germs exhibit brain gene expression anomalies and neuropathology with abnormal transcriptome patterns in the hippocampus, striatum, amygdala and frontal cortex [70]. Specific genetic mutations are implicated in neuronal transmission, steroid hormone metabolism and synaptic long-term potentiation. Numerous studies have reported that the alterations in BDNF and synaptic protein levels are associated with the microbiota [64,67,73,74]. Ogbonnaya et al. showed elevated levels of corticosterone and adrenocorticotropic hormone due to stress-induced amplification of the hypothalamic-pituitary-adrenal axis [75].

Table 2
Animal models relate ASD to dysbiosis of the gut microbiota.

Model of animal	Behavior	Outcomes	Ref.
Mice	ASD-like behaviors	P-Cresol, a drinking water drug, disrupted social behaviors in mice, leading to increased fecal p-Cresol content. Colonization with untreated microbiota restored excitability and social interaction deficits.	[76]
GF mice	Impaired innate immune system	Oral administration of microbial SCFAs to GF mice has been found to control the impaired microglia maturation observed in GF mice.	[77]
Sprague Dawley rats	Depressive-like behaviors	Sprague Dawley rats administered Antibiotics showed differences in brain serotonin levels, spatial memory deficiencies in adults, and increased depression-related behaviors.	[78]
GF mice	Enhanced permeability of the BBB	GF adult mice exposed to *Bacteroides thetaiotaomicron* or *Clostridium tyrobutyricum* showed enhanced BBB integrity and increased transcription of claudin−5 and tight-junction occludin proteins.	[79]
Mice	The connection between anxiety and depression-related behaviors	*Lactobacillus rhamnosus*, a probiotic, was administered orally to stress model mice, activating GABA receptors and reducing stress.	[18]
GF mice	Social interactions and behaviors	Human microbiota from ASD or TD siblings was transplanted into GF mice, revealing similar behaviors and alternative splicing of genes in ASD mice's brains.	[80]
MIA mouse	Behaviors like ASD	MIA mice's offspring displayed reduced cytokine/chemokine levels, increased IL−6, intestinal barrier disruption, and altered gut microbial metabolites. Oral treatment with *Bacteroides fragilis* reduced ASD-associated abnormalities.	[81]
Rats	Behaviors like ASD	PAA injection in rats resulted in elevated locomotor activity and ASD-like behavior, with notable changes in plasma phospholipid species and brain composition.	[82]
GF mice	Response of stress	GF mice treated with SPF microbiota showed reduced BDNF expression and increased ACTH and CRH secretion. At the same time, stress-related hormonal abnormalities were partially repaired by SPF microbiota, especially if administered early in life.	[83]

5. The promising potential of microbially mediated therapies in ASD

The prevalence of ASD has increased and patients often suffer from gastrointestinal impairments. Gut microbiota, immunity, metabolism, neurodevelopment and behavioral symptoms are associated with the development of ASD [84]. Microbiome varies in individuals with ASD and control groups, possibly due to methodological limitations and intrinsic variability. Dietary adjustments and xenobiotic exposures may permanently modify gut microbiota [85]. A clinical trial on ASD children found that vancomycin treatment improved behaviors, but these disappeared when stopped, suggesting the microbiome may contribute to the severity of the disorder [46]. Specific case studies also associate the use of antibiotics with improvements in co-morbid illnesses and ASD behaviors [86]. Several studies have shown that d-cycloserine and minocycline are effective in treating behavioral symptoms of ASD in animal models and clinical trials [87–89]. Research suggests microbe-mediated therapy could potentially benefit individuals with ASD by regulating gut microbiota despite ASD patients often consuming gluten and casein-containing diets [90,91]. Enhancements on a global scale while following a ketogenic diet [92] and prospective benefits of a GF diet on GI symptoms and behavior in ASD [93] have been documented in studies. A comparison of the treatment group with the control group over a year revealed superior results with developmental age and ASD symptoms [94]. Another study found clinical variability in ASD may identify individuals who might potentially gain advantages from specific diets. Probiotics are being tested in clinical trials to determine their potential for treating gastrointestinal issues and many trials have provided positive results [95]. Probiotics with a single beneficial bacterial strain are effective for treating IBS. Arnold et al. have suggested multistrain formulations are more effective for treating ASD [96]. Combining a single strain (*B. infantis*) and colostrum requires further investigation [97]. Ghaleiha et al. also indicate that more research is required to determine whether the reductions in irritability and hyperactivity/noncompliance observed with minocycline as an adjuvant to risperidone are long-lasting [98]. A pilot study found no impact of D-cycloserine on ASD social deficits, but the social skills training program improved the cohort overall [99].

Kang and colleagues demonstrated that Bifidobacterium, Prevotella and Desulfovibrio populations remain intact for two years following treatment for ASD symptoms. They used microbiota transfer therapy (MTT) to treat autism spectrum disorder symptoms, involving antibiotics, bowel preparation, proton-pump inhibitors and fetal microbiota transplantation, resulting in long-term improvements [100]. Furthermore, Yang et al. found that gut microbiome therapies, including fecal microbiota transplantation, vitamin A supplementation, probiotics, and prebiotics, can significantly improve the gut microbiota of autistic children and ameliorate their symptoms [101]. The gut microbiota and inflammation play an essential role in developing the nervous system in ASD. It is believed that immunological function, neurodevelopment and changes in the microbiome may be intricately linked with ASD during pregnancy. Current studies suggest that a better understanding of these pathways could clarify the pathophysiology of the brain, provide insight into the neural basis of ASD symptoms, and facilitate the development of new therapeutic strategies [102].

6. Etiology of ASD

The pathophysiological mechanisms of ASD remain a mystery that has not been fully understood. The precise molecular mechanism behind the etiopathology of ASD remains challenging due to its diverse presentation, risk factors and comorbidities (Fig. 4). However, genetic and environmental factors can be used to categorize the etiology of ASD. The development of ASD can be attributed to a variety of environmental and genetic factors. Multiple studies have indicated that a complex interplay between genetic and environmental factors within the gut microbiome influences ASD [103–105]. Researchers have found that genetic factors remain significant and consistently balance environmental factors despite increased clinical diagnoses of ASD [106]. Environmental factors, including zinc deficiency, parent age and viral infection, can increase the susceptibility of ASD, while genetic factors primarily induce neurodevelopment, communication and social interaction [107]. Clinical geneticists are increasingly referred for evaluation due to accurate diagnosis, assessment options, patient interaction, laboratory testing and syndromic and metabolic disorders [108].

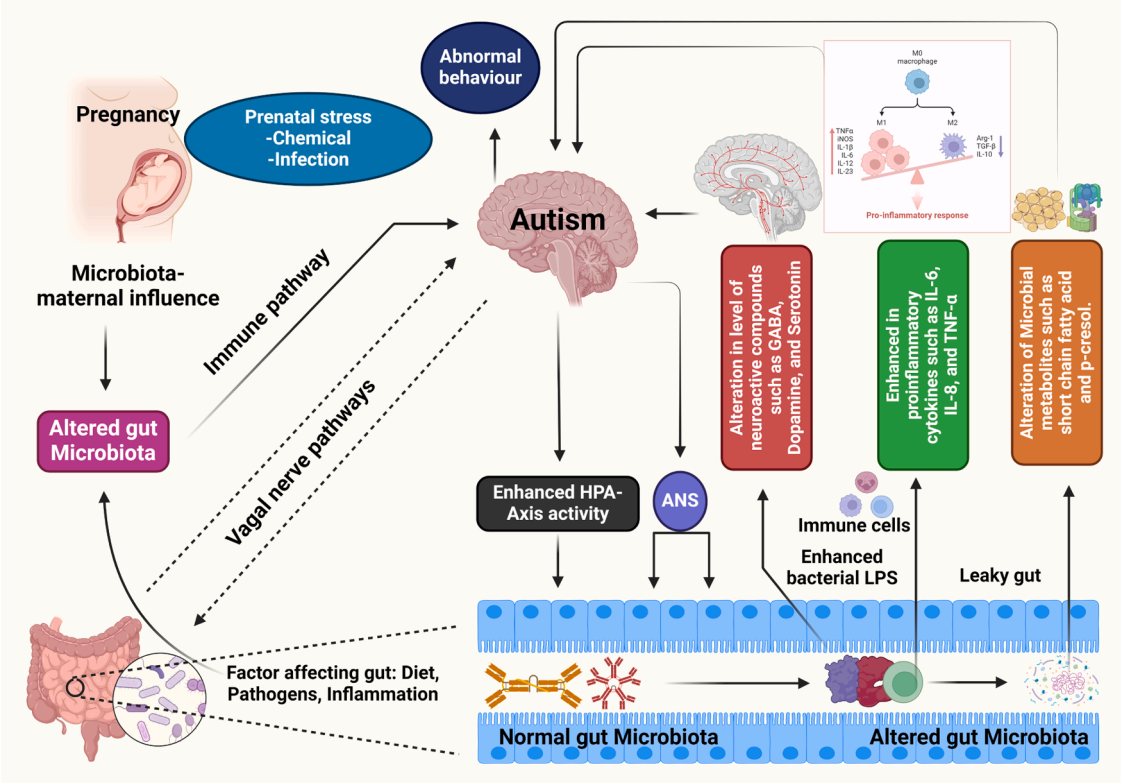

Fig. 3. The gut-brain axis can be affected by alterations in the gut microbiota during pregnancy such as dysbiosis, which may further contribute to the development of ASD.

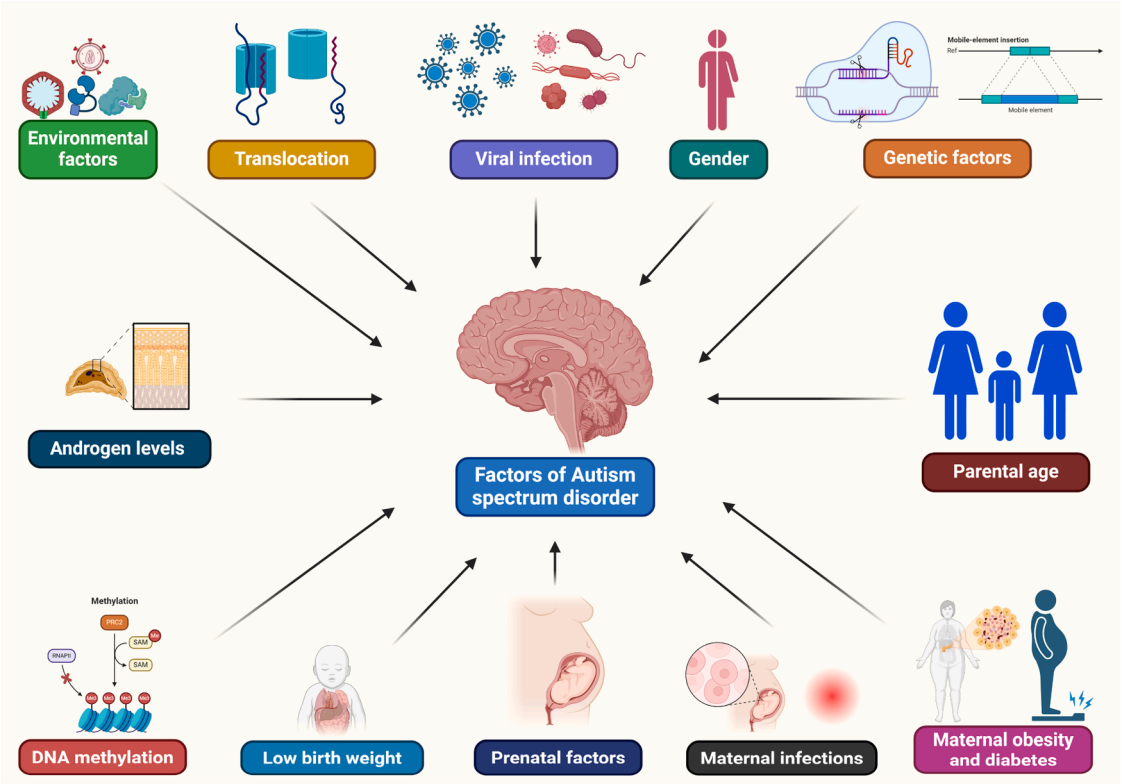

Fig. 4. Genetic, environmental and epigenetic risk factors contribute to the development of ASD.

6.1. Environmental factors

The development of ASD has been connected to a diverse range of environmental factors. The environment is thought to play an essential role in the development of children from conception to postpartum. Studies have revealed that pre-conceptional advanced father and mother ages (above 50 and 40, respectively) impart a significant risk for the development of ASD [109,110]. Pregnancy during the first and second trimesters is associated with ecological considerations, including maternal infections, cardiometabolic conditions, antiepileptic drugs, toxins, lifestyles, premature birth, oxygen deprivation, low birth weight and Apgar scores [111,112]. Several lines of studies have revealed that postnatal congenital infection, neonatal hypoxia, steroid treatment in deficient birth weight infants and jaundice are more common in ASD children [113,114]. In addition, various factors including maternal immune activation or direct biological effects on the development of the brain in the fetus may contribute to the activation of neuroinflammatory responses and the dysregulation of essential genes [112,115]. Studies on environmental factors in mothers and children with ASD suggest that environmental factors are more significant than the genetic variance [104,116,117].

6.2. Epigenetic factors

The concept of epigenetics explains the inherited nature of autism by altering gene expression without causing mutations or DNA sequence changes [105]. Gut microbiota metabolites, a gene-environment interaction, influence the incidence of ASD. Studies have shown that RNA interference, DNA methylation, and histone modifications are implicated in ASD [20,118–120]. Stress-regulating pathways and environmental factors throughout prenatal and postnatal periods have been proposed to have solid effects on neural function and behavioral outcomes [121,122]. BDNF is often associated with neuroinflammation and depression. In addition, BDNF regulates neuronal function, development and plasticity [123,124]. Recent studies on infants with ASD showed a considerably lower level of blood samples [125]. BDNF transcript variations exist in the amygdala area [64,70,126]. Accumulating studies show that microbiota regulates SCFA production by ASD-associated bacteria, which plays an important role in epigenetic activities [21, 119,127]. SCFA production may be increased in ASD children due to a general increase in SCFA synthesis [128,129]. ASD-associated microbial dysbiosis may lead to the overproduction of SCFA, altering nutrients, metabolites, DNA methylation and histone modification, potentially contributing to the development of ASD through epigenetic mechanisms [127].

6.3. Obesity

Obesity is a global health issue; although national statistics vary widely, 20 % of people are severely overweight [112]. The relationship between maternal weight and ASD prevalence is also inconsistent, as is the impact of obesity on autism and neurodevelopment [130]. The children of mothers who were both underweight and obese had an increased risk of ASD [131], suggesting that weight at either extreme of the weight continuum may be linked to autism. Children of obese mothers are 36 % more likely to suffer from ASD than children of normal-weight mothers [130]. Wang and colleagues discovered the susceptibility to autism when maternal obesity is present and women gain weight while pregnant [132].

6.4. Sex steroids

Elevated prenatal contact with sex steroids may alter hormones and increase the likelihood of ASD [133]. Abnormalities in the male brain primarily cause the progression of autism [134]. There is evidence to support this theory that prenatal testosterone influences eye contact, vocabulary size, limited interests, mentalization, compassion and autistic characteristics [135]. Fetal testosterone influences individual brain variations, similar to sex-biased developmental disorders including sexual dimorphism and autism [136–138]. Single nucleotide polymorphisms in the sex steroid synthesis genes (CYP19A1, CYP17A1, CYP11B1, and ESR2) were linked to autism features and autism with no cognition and high oral communication abilities [139]. Sex steroids (testosterone, androstenedione, 17α-hydroxy-progesterone, and progesterone) and cortisol were measured in amniotic fluid samples in males from the Danish Psychiatric Central Register and the Danish Historic Birth Cohort using liquid chromatography-tandem mass spectrometry [133]. A recent study found that the majority of neurodevelopmental disorders affecting men, including ASD, are caused by exposure to fetal testosterone [140]. ASD has been studied as Polycystic Ovary Syndrome (POS). This disease affects at least 5 % of women of childbirth age and causes changed prenatal exposure to sex hormones that result in a pattern of higher androgens in females [141]. A higher probability of ASD for both male and female children of mothers with POS was found in research conducted to investigate the complete population of Swedish children between the ages of 4 and 17; comorbid obesity further increased the risk of autism [142]. Based on the same population, another study found that hirsutism in the mother, another symptom linked to hyperandrogenism, increased the risk of autism in children [143]. Palomba et al. found that daughters of mothers with POS had higher levels of autistic characteristics compared to unimpacted mothers [144]. Studies showed that women with POS have a higher incidence of ASD [145] and that women with ASD are more likely to experience steroid-related diseases [146].

6.5. Infections and immune activation

The immune system and infections play a significant role in the development of autism, as evidenced by the correlation between congenital rubella infection and autism [147,148]. Inflammation, cytokine dysregulation, anti-brain autoantibodies and other viral and bacterial infections including rubella promote the development of autism [149,150]. Specifically, children with autism are twice as likely to experience maternal influenza [151]. A study in Sweden found a 30 % rise in ASD diagnoses for every maternal inpatient infection diagnosis in a nationwide register-based birth cohort from 1984 to 2011 [152]. Atladóttir and co-workers found that a higher susceptibility to ASD was associated with disease in all trimesters of pregnancy [149]. The combination of infections and intellectual disabilities may increase the likelihood of ASD [152]. ASD cases showed a high prevalence of CMV, but the limited number of investigations affected its reliability [153]. Pregnant mothers with autistic children have increased levels of inflammatory markers and antibodies, suggesting maternal infection pathogenesis may not be directly linked to viruses or bacteria [154,155]. The rhesus monkey model showed maternal immune activation in offspring, causing atypical behaviors, communication issues and social disruptions, similar to human autism [156]. Improved animal models and paired phenotyping may enhance the reproducibility and application of findings on ASD in understanding the disorder [157]. Different cytokine profiles may induce neurodevelopmental disorders such as autism. However, current studies are limited to rodent models [81,158]. Cytokines linked to ASD are found in maternal, placental and fetal pathways, with maternal cytokines crossing the placenta, placental immune activation causing inflammation and fetal immune and gene dysregulation [115]. Maternal antibodies in serum or plasma, lasting years after infection, may indicate a predisposition to ASD due to diseases or autoimmune conditions [159]. Maternal autoantibody exposure in pregnant mice leads to neurodevelopmental adversity, decreased motor control, sociability, behavioral exploration, anxiety, altered sensory perception and stereotypies [160–162].

7. Signaling pathways associated with ASD based on the composition of the gut microbiome

7.1. Immune system pathway

The gut and brain communicate two-ways through the immune system and microbiota. Several microbes in the gut play an essential role in maintaining immune hemostasis including pathogenic and essential microbes [163,164]. Additionally, various immune cell types including gut-associated lymphoid tissue (GALT) are present in the mucosal surface layers of the gut [165]. GALT produces immunoglobulins (IgA) by using lymphocytes [166]. Microbial cells in the ENS can alter the innate immune response when connecting with dendrites. IgA levels were shown to be elevated in ASD individuals in specific investigations [167]. A growing body of research has reported that individuals with ASD have been discovered to exhibit various inflammatory markers [168,169]. A pattern of immune response activation in individuals with ASD involves the activation of microglial cells accountable for pathogen eradication [170]. People with autism have been found to have altered gut microbiota, which may result in immune system defects. These GF mice also displayed inadequate immunological response against viral infection and abnormal social avoidance behavior [77].

7.2. Gut permeability pathway

The microbiota and its metabolic products are essential in regulating the integrity and function of the gut epithelial barrier [171]. A compromised intestinal barrier can increase gut microbial components, trigger immune responses and cross the BBB, which further induces inflammation in the body and CNS [172,173]. It was discovered that ASD patients had far higher serum levels of LPS than did healthy controls. A lower score for social interaction has been observed in ASD patients [174]. Under physiological conditions, the mechanisms of lipoprotein transport may allow LPS to enter the brain [175]. LPS enters the body and activates the NF-κB signaling pathway, which stimulates microglia and promotes the loss of neuronal cells [176], resulting in neural impairment, behavioral changes and neuroinflammation. Foley and co-workers reported that regular injections of LPS into pregnant rats were found to induce hyperlocomotion and social impairments, characteristics associated with ASD [177]. Settanni et al. report that individuals with ASD exhibit abnormal intestinal permeabilities spanning 43–76 % [178]. Furthermore, 9 out of 21 individuals diagnosed with autism exhibited intestinal permeability compared to 40 non-autistic children [179]. A pioneering study found that whereas normal people had altered gut permeabilities of 4.8 %, ASD individuals and their first-degree relatives had altered gut permeabilities of 36.7 % and 21.2 %, respectively [180]. Male BTBR mice showed a significant drop in mRNA levels of occludin and zonulin, crucial proteins for regulating intestinal permeability [181,182]. Another study by Magistris and co-workers investigated that autistic patients on a gluten- and casein-free diet showed much lower intestinal permeability [180].

7.3. Neuronal signaling pathway

Several neurotransmitters are produced by the intestinal microbiota such as GABA, acetylcholine, and serotonin, which can influence the activity of the ENS and CNS [183]. The neurotransmitter serotonin plays an important role in the regulation of mood and gastrointestinal activity [184]. Serotonin production in the human body is primarily controlled by enterochromaffin cells in the gastrointestinal tract (95 %), while the brain produces the remaining 5 % [185]. Serotonin synthesis is found in the guts of bacteria such as *Candida*, *Escherichia*, *Enterococcus* and *Streptococcus* [186]. Several lines of studies have indicated that the gut microbial mix influences the synthesis and secretion of 5-HT by Ecs [62]. A study indicated that antibiotic-induced gut microbiota depletion in mice is linked to reduced learning and increased depressive-like behaviors [78]. Additionally, a correlation was shown to exist between the blood level of 5-HT and the intensity of gastrointestinal symptoms [59]. However, tryptophan, an essential amino acid, may also be converted into serotonin [187]. Current research indicates that reduced tryptophan intake increases autistic behavior, suggesting that gut microbiota significantly regulates the production and equilibrium of 5-HT [188]. The primary inhibitory neurotransmitter in the brain is GABA, an amino acid. GABA receptors are one of the most important aspects of the neurophysiology of persons with ASD [189]. GABAergic transmission may be disrupted in people with ASD, affecting communication, processing of information and response to stimuli [190]. *Bifidobacterium* and *Lactobacillus* species produce GABA [191]. Bravo and colleagues found the colonization of *Lactobacillus rhamnosus* JB-1 in mice decreased the level of stress and depression and increased the number of GABA receptors in the vagus nerve [18].

7.4. Neuroendocrine signaling pathways

The brain can also regulate the activity of intestinal effector cells, gut permeability, motility, mucus and immunology through the hypothalamic-pituitary-adrenal (HPA) axis, which results in the translocation of gut microbial components. The pituitary gland secretes adrenocorticotropic hormone (ACTH) due to releasing corticotrophin-releasing hormone (CRH) from the hypothalamus. Glucocorticoids and cortisol are released from the adrenal glands, which affect various organs, including the brain [172,183]. The colonization of *Bifidobacterium infantis* was found to correct abnormal hormone levels in young mice. Sudo et al. showed decreased expression of BDNF and NMDA receptors in the cerebral cortex and hippocampus. The alteration in the expression and release of CRH led to a modification in the HPA axis function [83]. Studies on individuals with ASD have revealed altered mRNA levels in the glucocorticoid receptor and CRH receptor 1, indicating systemic changes [192].

7.5. The metabolic pathways

Microbiota produces compounds that reach host immune cells, alter metabolism and regulate the vagus nerve and ENS, directing signals to the brain [193]. The microbiota produces a variety of metabolites including phenolic substances, FAAs and SCFAs [194]. SCFAs promote energy balance and glucose metabolism and lower the risk of cancers [195]. Furthermore, studies have found that SCFA regulates the release of T-cell cytokine, which promotes the immunological response [196]. Previous studies have indicated that butyrate levels decreased significantly in individuals with ASD while acetate and propionate levels increased [52,197]. The severity of ASD has been correlated with the elevations of PAA. During an experiment, rats were given PAA for eight days and displayed hyperactivity and stereotypy in their movements [82]. People with ASD have altered blood phospholipid profiles and gastrointestinal symptoms. A positive impact was observed when butyrate was administered to children with ASD [198]. Furthermore, Rose and her co-workers have reported that butyrate can enhance mitochondrial function during physiological stress and shield cells from oxidative damage [199]. In addition, Downs et al. showed that butyrate enhances the permeability of BBB, which could reduce ASD deficits caused by PAA [200]. The presence of bacteria such as *Clostridium tyrobutyricum* and *Bacteroides thetaiotaomicron,* in GF *mice* increases the expression of occludin, which is associated with the reduction of BBB permeability [79]. Additionally, it was found that children with ASD had higher rates of p-Cresol and its conjugated derivatives in their urine samples [201]. P-Cresol is involved in numerous metabolic processes in the human body, which can exacerbate the severity of ASD and gastrointestinal function [52]. The most typical representative microorganism is *Clostridium difficile*, which produces p-Cresol. Altieri et al. showed that the p-hydroxy phenylacetate (p-HPA) enzyme could be induced by *C. difficile*, which promotes the fermentation of tyrosine to

produce p-Cresol [202]. Bermudez et al. reported that Mice fed p-Cresol in their drinking water for four weeks exhibited abnormal social behavior and altered gut flora composition [76]. Lin et al. showed that the p-Cresol intervention reduces the excitability of animal dopamine neurons [203]. The p-Cresol affects behavior by altering gut microbiota composition, inducing behavioral abnormalities in mice treated with p-Cresol and restoring normal social behaviors through microbial transfer [76].

8. The symptomatology of ASD and gut microbiota

8.1. Gut microbiota and behaviors related to ASD

Social behavior and gut microbiome are strongly related in the animal kingdom [204]. A study found a correlation between gut bacteria and behavior in rat models [205]. These investigations have used both top-down (e.g., beginning with a genetic mouse model and studying their gut microbiome) [54] and bottom-up (e.g., changing the colonization of germ-free mice by microorganisms) [63] methodologies. Another study demonstrated the crucial role of healthy microbiota in societal interaction in animal models, as many behavioral abnormalities were restored when fecal bacteria from neurotypical mice were introduced. The gut microbes influence the symptoms of ASD (Fig. 5). Additionally, a study [54] in BTBR mice found altered abundance levels of 18 gut bacterial species, linked to behavioral and physiological abnormalities and lower *Bifidobacteria* and *Blautia* species, crucial for optimal gastrointestinal and metabolic functioning. Furthermore, a study [206] of the fecal samples of children with ASD and neurotypical controls found that the ASD group had lower *Bifidobacterium* abundances. The gut in BTBR mice showed abnormally high abundances of *Lactobacillus*, *Bacteroides*, *Desulfovibrio* and *Akkermansia* bacterial taxa [54]. Studies on mice and humans suggest that gut microbiota-associated metabolites contribute to symptoms of ASD and GI disorders [30,207,208]. Needham et al. found significant differences in fecal and plasma metabolomes between typically developing and ASD children, suggesting microbial abnormalities may not be exclusive to ASD patients with GI dysfunction [208]. The Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) are two clinical ASD assessments that measure clinical behaviors [208]. Mice colonized with ASD microbiota showed distinct metabolome profiles, decreased mobility and communication and increased repetitive behavior compared to lineage colonized with TD controls [80]. Furthermore, ASD bacteria have shown reduced sociability, ameliorated hyperosmia and dysregulated metabolic pathways and metabolites [208,209].

8.2. Gut microbiota and GI impairment in ASD

Given that 46–84 % of people with ASD have GI symptoms (namely, diarrhea, constipation and abdominal discomfort) [210], it is possible that gut dysbiosis is significant for ASD patients who have GI distress. The gut microbiome of ASD children showed abnormal metabolites and specific taxa compared to healthy controls [30,207,211]. The precise microbial composition linked to ASD is challenging due to inconsistent results at various and diverse levels [30]. Many factors contribute to the lack of agreement in studies including sample collection, preprocessing, statistical analysis, participant diet, age, gender, specimen type and gastrointestinal disorders in individuals with ASD [62].

8.3. Reduction of symptomatology of ASD via gut microbiota therapy

Research explores probiotics as a potential treatment for ASD based on previous research on the relationship between microbiome and behavioral symptoms [212]. Many studies suggest that people with ASD and TD can benefit from probiotics, which can ameliorate gastroenteritis symptoms [213–215]. Thus, probiotics have also been investigated for

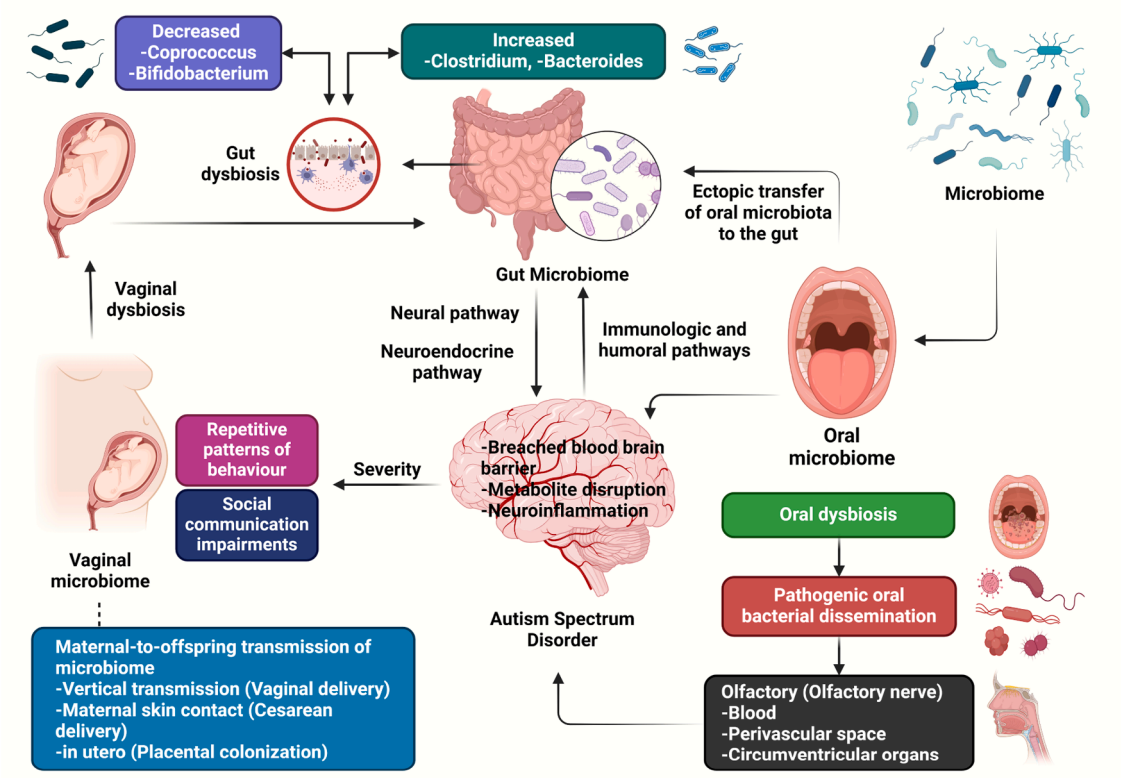

Fig. 5. The gut microbiome and brain interact in ASD, with potential mediators including neuronal, neuroendocrine, immunologic, and humoral pathways. ASD may be affected by oral microbiota and dysbiosis since the microbiome determines early intestinal colonization. The ectopic transfer of pathogenic oral bacteria via the olfactory nerve disrupted the BBB and the oropharynx mediates the interaction of the gut-brain axis.

their potential to improve the behavioral symptoms of ASD in mouse models. Using a maternal immune activation (MIA) mouse model, a study [81] observed that after the prenatal mother administered the viral polyinosinic-polycytidylic acid (poly I: C) at critical stages of neural growth, the offspring exhibited several fundamental characteristics of ASD [216]. Hsiao et al. reported that MIA children had increased metabolomics, altered microbiomes, enhanced intestinal permeability and improved behavioral impairments associated with ASD [81]. Administering the gut commensal *Bacteroides fragilis* orally restored intestinal permeability, enhanced blood metabolite profiles and gut microbiota and reduced the symptoms of atypical anxiety, repetitive behaviors and sensorimotor behaviors in the MIA offspring [81]. Several microorganism strains have been shown to improve social behavior in preclinical studies significantly, but not all social symptoms have been improved [81]. Research has shown that different *Lactobacillus* strains can mitigate social deficits in animal models [205]. In addition, Buffington and colleagues discovered that *L. reuteri* could alleviate social deficiencies in offspring born to mothers on high-fat diets, rodents with gut-microbial changes that negatively impact their social functioning [217]. A pioneering study also indicates that an *L. plantarum* PS128 intervention can reduce behavioral issues in children with ASD and alleviate social communication impairments, thereby supporting the use of *Lactobacillus* strains [218].

Kang et al. found that a gut cleanse, acid-suppressant treatment and antibiotics combined effectively improved symptoms and social skills deficiencies in 18 ASD children with GI abnormalities [219]. A growing body of research indicates that the metabolite profiles of the ASD group were comparable to the TD group after MTT [220,221]. Chen et al. showed moderate improvements in social conduct and notable enhancements in personality deficits linked to ASD, especially in behaviors connected to anxiety and repetition [222].

9. The potential therapeutic applications of gut microbiota-targeting ASD

Gut microbial-targeting therapy could potentially replace antibiotics as a treatment for ASD, affecting gut balance, but medical conditions or compromised immune systems should avoid probiotics [223]. Prebiotics improve digestive health by promoting beneficial bacteria growth and serving as a food source for commensal bacteria, but there is limited research on their use in ASD patients [197]. A study showed the positive effects of omega-3 fatty acid supplementation, ketogenic diets, casein and gluten-free diets regarding the well-being of children diagnosed with ASD. It found the potential adverse effects of the GFCF diet, including amino acid deficiency and calcium shortage, potentially lowering bone density and increasing fracture risk in individuals with ASD [224]. MTT can regulate the gut microbiota of autistic people and lessen symptoms related to ASD [219].

9.1. Prebiotics

Prebiotics are primarily fructo-oligosaccharides, galacto-oligosaccharides, inulin and lactulose. Prebiotics are fermented ingredients that alter the composition and activity of the gut microflora, providing health benefits to the host [225]. The body already contains two beneficial bacteria, lactobacilli and bifidobacteria stimulated by prebiotics. Numerous studies have shown that the fermentation of prebiotics by bacteria produces SCFAs, which have been associated with positive health effects [226,227]. Additionally, the prebiotic Galacto-oligosaccharide (B-GOS) increased the abundance of Bifidobacterium spp. in stool specimens from children with and without ASD [197]. Probiotics and prebiotics may benefit children with ASD with digestive or behavioral issues, but further research is needed due to limited randomized controlled trials and treatment durations [228]. A meta-analysis investigating the efficacy of probiotics and prebiotics in reducing gastrointestinal issues, comorbid psychopathology in ASD, and ASD symptoms in children found no significant improvement [229].

Diet, particularly macronutrients, may significantly improve the functions of gut microbiota. Inflammatory conditions can negatively affect memory when consuming Western-style eating [230]. Gilbert et al. demonstrated that high doses of polyunsaturated fatty acid treatment reduced depression in rats [231]. Savignac et al. found [232] that oligosaccharides have neurotropic effects on rat models and have been shown to stimulate the growth of naturally occurring good gut bacteria, including *Lactobacilli* and *Bifidobacteria*. Schmidt et al. also found that the Bimuno®-galactooligosaccharides supplement improved the processing of positive vs negative attentional vigilance in healthy humans and reduced the neuroendocrine stress response [233]. Dinan and colleagues have shown that prebiotics may enhance neuropsychiatric treatment and brain function by modifying gut flora, focusing on their impact on behavioral phenotypes and neurological and endocrine systems [234].

9.2. Probiotics

Probiotics are live microorganisms that improve intestinal transit regulation, enterocyte turnover rate, and the synthesis of SCFAs in humans [235]. Probiotic supplements containing Bifidobacterium and Lactobacillus stimulate beneficial microbe growth and metabolism, improving host health and functions [236]. Probiotics, prebiotics, and synbiotics have been demonstrated as therapeutic interventions for ASD [237,238]. Probiotics are a class of live microorganisms found to restore gut microbiota balance and improve health conditions. In addition, probiotics alleviate gut inflammation by reducing intestinal barrier permeability, mitigating inflammation caused by cytokines, and possessing immunomodulatory effects [239]. A study found that medication effectively treated severe cognitive impairment in ASD patients, reducing gastrointestinal and autistic symptoms and normalizing Bacteroidetes/Firmicutes ratios. Regular probiotics reduced Bifidobacterium and Desulfovibrio spp. in autistic children's feces [240]. Fang and colleagues have shown that probiotic administration significantly reduced TNFα levels and has been correlated with altering the gut microbiota composition in children with ASD [241]. Researchers found that children with ASD who received oral supplementation with Lactobacillus acidophilus had reduced levels of D-arabinitol in their urine, improving their compliance with instructions [242].

Probiotics improve behaviours associated with ASD in mice and children [81]. Several studies have shown that intestinal *B. fragilis* PSA may significantly promote the development and function of the host immune system [243,244]. PSA mediated probiotic impact on ASD behavioral changes in MIA children, revealing normal blood metabolites in previously altered MIA children and a single serum metabolite in mice with behavioral abnormalities [81].

A study on maternal obesity in mice found that children with high-fat diets exhibit social and behavioral impairments. *Lactobacillus reuteri* restored the activities of the dopamine reward system and oxytocin levels in the gut microbiota. However, gut microbiome alteration did not correct repetitive behaviors [217]. Gram-positive *Lactococcus reuteri* bacteria develop the gastrointestinal systems of animals. Studies have shown that *Probiotic L. reuteri* protects the host against harmful infections and regulates the immune system [245,246]. *L. reuteri* has been extensively researched to treat pediatric diarrheal diseases and has been shown to ameliorate the duration of symptoms significantly [247]. It has also been found that *L. reuteri* increases the levels of oxytocin, a hormone that regulates social behavior [248]. Furthermore, a study showed that the administration of oxytocin effectively improved behavioral and electrophysiological abnormalities in MHFD pups, comparable to that of *L. reuteri* treatment [217]. A unique category of probiotics with promising medicinal uses in treating psychiatric diseases was called "psychobiotics" [249]. Probiotics may improve the behavioral symptoms of ASD and mediate the symptoms in GI in diverse populations, possibly due to varying microbial targets [250]. Moreover, Probiotic

supplementation may effectively reduce symptoms of ASD, particularly in recurrent and resistant *Clostridium difficile* infections [251].

10. Novel treatments for ASD that focus on the gut microbiota

The "gut-brain axis," a bidirectional communication mechanism between the gastrointestinal tract and the brain, has garnered significant attention in the past 20 years. Researchers have recently discovered that gut microbiota regulates brain health and multiple diseases [163]. The gut microbiota can affect the functions of the brain by regulating neurological, endocrine, and immunological processes [252]. Several studies have investigated the effect of dysbiosis on neuropsychiatric diseases following the demonstration of the potential role of the gut microbiome on the brain. Growing evidence has demonstrated that the absence of a gut microbiome significantly impacts the brain and behavior [63,67,70]. Additionally, alternative splicing of genes associated with ASD was observed, indicating that a pathogenic microbiota could participate in the pathogenesis of the disorder [80]. A three-month supplement formula containing probiotics, *Bifidobacterium longum*, *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* significantly improved gut microbiome and fundamental symptoms in children with ASD [253]. These strains include *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium infantis* and *Lactobacillus delbrueckii* subspecies. Bulgaricus, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus plantarum* and *Lactobacillus para-casei*. A study found no significant difference in inflammatory biomarker levels and autism severity, but individuals with ASD and GI symptoms experienced varying outcomes from DSF supplementation compared to a placebo. This study showed that children in the first group improved their gastrointestinal symptoms, sensory profiles, and adaptive functioning post-treatment [250]. These outcomes are consistent with a prior pilot study conducted, which reported a reduction in GI symptoms in a group of children with ASD receiving DSF treatment [96].

A study involving 16 ASD patients and 10 placebo participants showed that probiotics plus FOS supplements significantly improved gut microbiota and fundamental signs of ASD. The probiotics+FOS group showed substantial enhancements in GI and basic signs of ASD, while the placebo group did not show significant changes. The intervention reduced high levels of *Clostridium* and *B. longum* in the gut microbiome composition and improved levels of SCFAs and associated metabolites in plasma neurotransmitters. Wang et al. showed that the probiotics+FOS intervention improved leaky gut [254]. The goal is to enhance and possibly normalize the recipient's microbiome by transferring gut bacteria from healthy donors [225,264]. The MTT treatment significantly improved gastrointestinal symptoms and increased essential bacteria and gut flora diversity, with no significant side effects reported after eight weeks [219].

10.1. Fecal microbiota transplant

FMT is extensively researched for treating recurrent *Clostridium difficile* infection and other gastrointestinal issues, unlike probiotics with numerous bacterial species [255,256]. A recent open-label trial found that gut microbiota balance can be restored in children with ASD, resulting in significant improvements in gastrointestinal and ASD-related symptoms. This marks the first clinical trial to use FMT treatment for ASD in humans [219]. In addition, several lines of studies have revealed that the long-term safety and tolerability of FMT treatment in ASD patients require a large sample size due to the adverse effects observed in both this trial and a prior investigation [219,257].

11. ASD and the modification of the gut microbiome

The changes in gut microbiota may negatively impact neuropsychiatric diseases [258,259]. A study published in 1998 suggested that *Clostridium tetani* may induce the development of ASD by affecting the gut microbiota [260]. Another study demonstrated that oral vancomycin alleviated gastrointestinal and behavioral problems following six weeks of therapy in autistic children [46]. Furthermore, studies have indicated that gastrointestinal issues in ASD children may be linked to *C. perfringens*, a toxic substance that induces intestinal inflammation, particularly in those with GI symptoms [261,262]. Several microbes have been implicated in gastrointestinal disorders including intermittent diarrhea, foodborne illnesses and antibiotic-induced diarrhea [262]. Additionally, some investigations found that autistic people had greater levels of *C. difficile* than did NT subjects [263,264]. A recent study by Svraka et al. found no significant statistical difference between the three groups, even though autistic patients and their siblings had a higher *C. difficile* proportion than unrelated controls [265].

Their abundance correlates significantly with the levels of fecal propionic acid (PPA) [258,266]. Current research suggests that high concentrations of PPA may cause behavioral abnormalities, while butyric acid is another essential SCFA with excellent anti-inflammatory and protective properties [266]. Accumulating studies have revealed that SCFA can enhance mucosal immunity [267,268], preserve the integrity of the intestinal epithelial barrier and regulate the expression of neurotransmitter genes [268,269]. A study showed that [267]. Akkermansia has also decreased substantially, particularly the species *Akkermansia muciniphila*, which is necessary for mucin breakdown and whose decline could lead to increased gut permeability [270]. Fungal components of gut microbiota were also observed in some of these studies. The phylum level did not reveal any statistically significant differences. Two investigations [56,271] found a substantial rise in the genus-level abundance of Candida, particularly in the species *C. albicans*. Previous studies have shown that autism behavior may result from the release of toxins and ammonia and the decreased absorption of nutrients and carbohydrates due to elevated *Candida* numbers [271,272]. Mucosal surfaces of the GI tract are frequently colonized by these fungi, which suppress and compete with the local flora [271]. Fungi and gut bacteria coexist delicately, which impacts each other. Many studies have also shown that antibiotic treatments can cause fungal commensals to blossom, inducing the colonization of *C. albicans* to obstruct healthy bacterial population restoration [56,259]. Zou et al. report that ASD increases the abundance of *Saccharomyces*, potentially causing human infections, despite previous findings suggesting a control group had higher *C. albicans* levels [272].

12. The outcomes of probiotic and prebiotic clinical trials for the treatment of ASD

Probiotic and prebiotic supplements may significantly improve the symptoms of ASD and regulate the dispersion of the gut microbiota (Fig. 6) [253,273]. A three-month probiotic regimen improved social networking and communication and reduced hyperactivity, sleep difficulties, and childhood autism scale scores in children with ASD [273]. Additionally, a pioneering study [253] found that following three months of probiotic therapy, children with autism experienced a drop in body weight, autism scale scores and GI symptoms but increased Bifidobacteria and Lactobacilli in their feces.

A randomized, double-blind, crossover study found that *Bifidobacterium infantis* and colostrum (prebiotic) effectively reduced core and GI symptoms in children with ASD [97]. Furthermore, a study demonstrated children with ASD showed altered beta and gamma band electroencephalography brain power following a 6-month probiotic therapy. Gamma and beta waves are associated with analytical thought, working memory activities, and sensory perception [274]. The combined interventional treatment can significantly reduce autistic symptoms. Patients with ASD were given probiotics or a placebo for 28 weeks in a prior randomized, double-blind, placebo-controlled, two-stage pilot study. Oxytocin was administered to both groups at the end of week 16. The group treated with oxytocin and probiotics significantly improved gastrointestinal symptoms and autism scale scores [275]. A trial

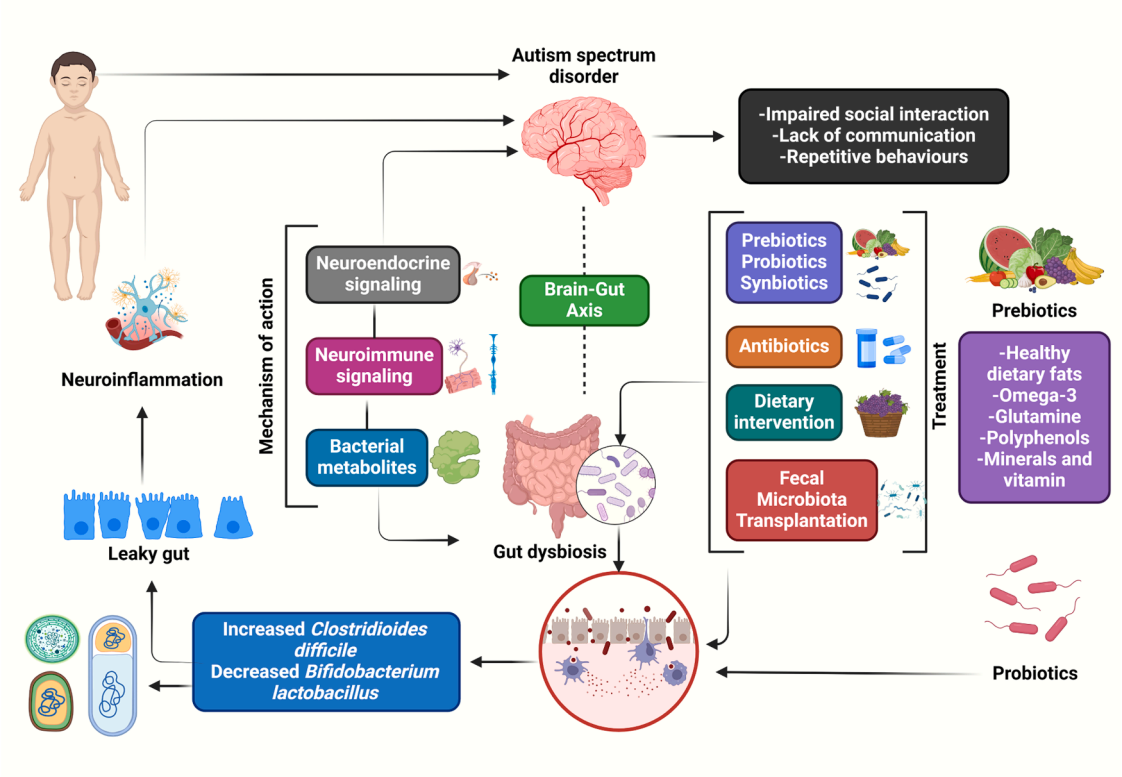

Fig. 6. ASD may be treated with prebiotics, probiotics and synbiotic supplements, antibiotics, fecal microbiota transplantation and dietary changes, which are influenced by gut microbiota functions.

demonstrated that probiotics and fructooligosaccharide intervention could enhance autism and gastrointestinal symptoms in children with ASD by modifying gut microbiome, fecal SCFAs and plasma serotonin levels [254]. Another study found that exclusion diets, which are gluten and casein-free, significantly reduced gastrointestinal symptoms in children with ASD. This therapy may lead to excessive amino acid excretion and nutrient loss. Patients showed a significant decrease in antisocial conduct and an increase in friendly gut flora when they combined an exclusion diet with prebiotics [276].

The effects of probiotics on autistic patients depend on their gastrointestinal symptoms. A randomized, double-blind, placebo-controlled trial involving children with ASD was conducted, with one group experiencing GI symptoms and the other without. Santocchi and co-workers have shown that probiotic medication improved adaptive functioning and sensory profiles in the GI group following five months. In contrast, the NGI group improved core autism and GI symptoms [250]. Furthermore, pioneering studies have shown a positive correlation between plasma 25(OH)D levels and the effectiveness of probiotic treatment in reducing the severity of ASD [277]. However, some studies failed to report significant impacts due to limited sample sizes and the insensitivity of the evaluation methods. A randomized, double-blind, placebo-controlled study found that probiotics did not decrease the Aberrant Behavior Checklist (ABC) ratings in children with ASD [218]. A significant decrease in impulsivity, hyperactivity, and oppositional/defiant behaviors was observed. A randomized, crossover experiment showed that children with ASD experienced improvements in their quality of life and emotional stability after 8 weeks of therapy [96].

13. Importance of microbial therapies for autism: research on animals, clinical trials and limitations

Studies have reported that the impairment of GI affects up to 40 % of children with ASD [278]. A growing number of physicians who treat these children believe there is a correlation between ASD and gastrointestinal disorders [279,280]. McMaster University researchers successfully transformed nervous mice into extroverted animals by altering gut bacteria, showing a strong connection between behavioral issues and gut microbiota [80]. Luna et al. found that gut microbial dysbiosis may potentially promote the emergence of neurobehavioral diseases [281]. The gut-brain axis and the functions of gut bacteria should result in fewer adverse effects when treating ASD [282]. Several intriguing discoveries about a microbiota-gut-brain axis have provided evidence that gut microbiota could induce neuropsychiatric symptoms in people with ASD [39,283]. For people with ASD, doctors typically advise a plant-based diet, probiotics and prebiotics. A non-digestible dietary component called prebiotics boosts the amount of commensal bacteria in the stomach (Fig. 7) [284,285]. A recent study found that a child with autism exhibited high levels of harmful bacteria in his intestine, such as *Clostridium tetani* [44]. Bolte et al. suggested that vancomycin treatment resulted in an instantaneous reversal of symptoms [260]. Moreover, the use of anti-Clostridium antibiotics has been shown to reduce the aberrant behavior of some autistic children [219]. The main drawback of vancomycin treatment is its inability to differentiate between beneficial and harmful bacteria. Further research necessitates identifying more effective antibiotics and reducing vancomycin usage during MTT pretreatment [286]. Fecal transplantation can significantly reduce symptoms of ASD in mice by increasing the number of symbiotic bacteria, including *B. fragilis* [287,288]. In addition, several studies have suggested that fecal transplant patients may consume beneficial bacteria as a potential treatment for ASD [289,290]. The intervention has been demonstrated to alleviate gastrointestinal and autistic symptoms [46]. A clinical trial of MTT involving 18 participants showed significant improvement in symptoms and increased Bifidobacterium and Prevotella abundances with most children reporting increased microbial diversity [286].

Kang et al. [100] have shown the long-term effectiveness of MTT for

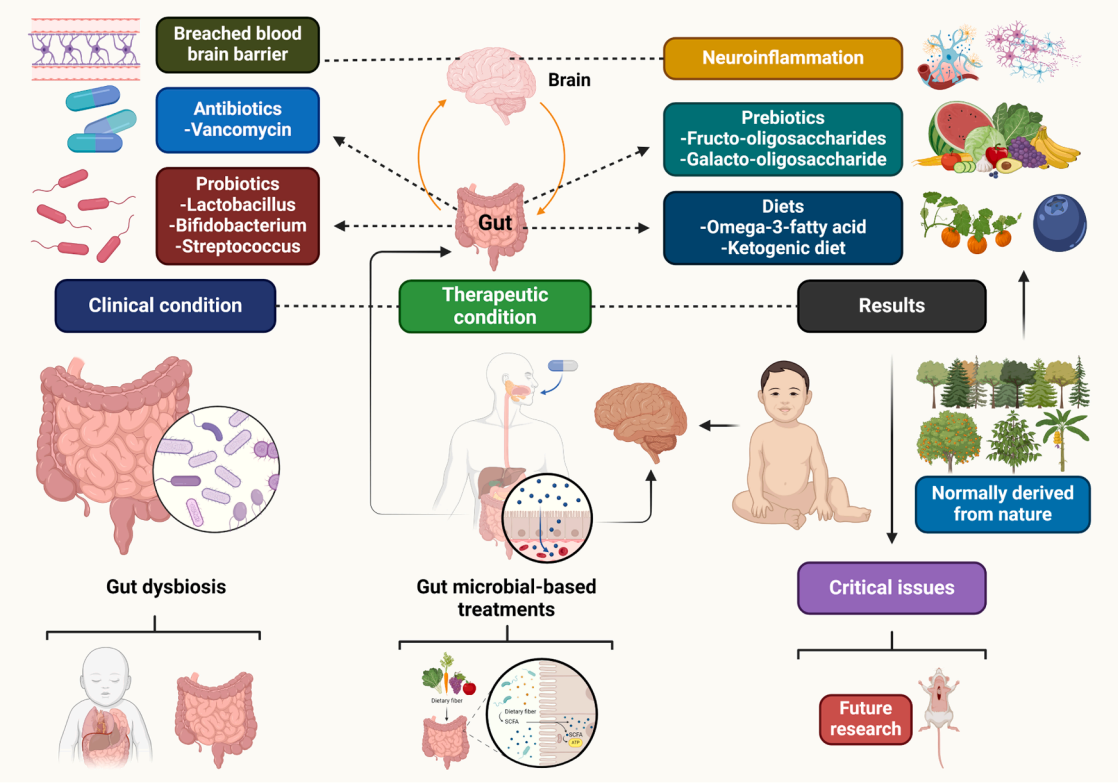

Fig. 7. Dysbiosis, an imbalance in gut microbiota, is linked to ASD. The changes in gut microbiota composition can exacerbate neurological symptoms, impacting immunological responses, inflammation, and neurotransmitter synthesis. Interventions targeting gut microbiota, such as probiotics, prebiotics and dietary changes, are being explored to improve the symptoms of ASD and restore microbial balance.

ASD patients with GI issues. Moreover, the gut ecosystem has developed an environment that encourages the growth of healthy microorganisms. A study found that 16S rRNA in bacteria can be used for taxonomic classification. Adams et al. showed that microbiota transplants can cause serious side effects, including fatal infections from the donor and resistant germs in the recipient [286].

14. Herbal medicine demonstrates hopes for the treatment of ASD

Natural products (Table 3), particularly plant resources, have shown potential effects for the treatment of autism and several NDs. However, their benefits and drawbacks have not been fully discovered or validated. Studies have indicated that psychoactive and herbal remedies can be effective treatment options for ASD [291]. ASD may be caused by OS, inflammation, neuronal degeneration and gut microbiota dysbiosis. Traditional Chinese medicine (TCM), an herbal remedy targeting gut bacteria, has shown promising results in treating ASD [292]. Liu et al. suggest that TCM including a diet containing whole grains and Chinese medicinal foods could potentially improve the management of ASD by enhancing gut microbiota, reducing endotoxins and increasing Bifidobacteria [293]. Another study comparing intestinal flora and microbiome with healthy controls found that Buyang Huanwu Tang (BHT) treatment normalized gut microbiota imbalance in autistic children. The BHT decoction, containing saponins, flavonoids and polysaccharides, regulated intestinal ecology and reduced the symptoms of ASD by interacting with the gut microbiota, according to the bioinformatics analysis [294]. The "Decoction of Four Nobles," an outdated remedy for constipation and diarrhea, can reduce ASD by interacting with gut microflora and normalizing it [293]. Studies indicate that phytochemicals such as curcumin, resveratrol, naringenin and sulforaphane activate the Nrf2/ARE signaling pathway, inhibit the generation of ROS and alleviate the symptoms of autism [295]. However, clinical trials are ongoing to explore alternative natural chemical treatments for autism to prove their effectiveness and understand their potential [296].

Table 3
Natural products are used to prevent and treat ASD.

Natural products	Major findings	Ref.
Curcumin	Curcumin improves the health of individuals with autism by reducing OS, mitochondrial dysfunction, protein aggregation, and inflammatory components. It impacts the CNS by modifying the GBA and increasing gut microbe diversity.	[297–299]
Luteolin	A 26-week luteolin treatment resulted in a decrease in TNF and IL−6 levels, leading to enhanced behavior. IL−6 and TNF levels in children with ASD can be used as reliable indicators to expect the positive effects of luteolin formulation.	[300]
Piperine	Effect on behavioral impairments and oxidative indicators in BALB/C mice with sodium valproate-induced autism.	[301]
Cannabidiol	A study involving 34 adult men, 50 % of whom have autism, found that cannabidiol altered the fractional amplitude of low-frequency fluctuations.	[302]
6-gingerol	6-gingerol-rich fraction has antioxidant properties, protecting against cerebral cortical damage and positively impacting ASD by balancing decreased GSH levels and lowering pro-inflammatory cytokine levels.	[303,304]
Vitamin E	Impact of vitamin E on the behavior of rats exposed to VPA during pregnancy, causing autism-like symptoms.	[305]
l-Theanine	L-theanine can reduce autism symptoms due to its similar structure to l-glutamate, which imitates its neuroprotective effects.	[306,307]

15. Conclusion and future perspectives

The therapeutic interventions based on gut microbiomes offer promise for therapeutic intervention and mechanistic understanding of the molecular pathogenesis and development of ASD. This review highlights the significant role of the gut-brain axis in regulating neurodevelopment and behavior in ASD. Immune signaling pathways and microbial metabolites regulate this axis. ASD patients have different gut microbiome profiles, suggesting that microbial dysbiosis may contribute to the pathogenesis of this disorder. Therapeutic approaches including probiotics, prebiotics and dietary changes, have shown potential in ameliorating the symptoms of ASD. However, further clinical trials are required to establish their safety and effectiveness conclusively. More research should focus on understanding the precise signaling pathways and molecular mechanisms by which gut bacteria influence behavior and neurodevelopment in the future. These pathways can lead to the development of more effective and accurate therapies. People with autism require customized therapies due to their unique gut microbiome compositions. Personalized therapies improve outcomes for patients with unique microbiological profiles, but longitudinal studies are needed to assess the long-term effectiveness and safety of microbiome-based therapies. Multi-omics technologies such as genomics, transcriptomics, proteomics and metabolomics, help us fully understand the complex connections between genetics, the gut microbiota, and environmental factors. The integrative method will facilitate the identification of new treatment targets and ASD biomarkers. Clinical trials utilizing standardized methods are crucial for demonstrating the effectiveness and safety of microbiome-based treatments. We need to design guidelines for these interventions to ensure the reliability and consistency of clinical practice. Researchers from various fields work together to understand and use therapeutics targeting gut microbiome in ASD, potentially revolutionizing treatment and enhancing well-being for affected individuals and families.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors have declared that no competing interest exists for publication.

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