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The Gut-Brain Connection: Investigating the Correlation between Autism Disorder and Gut Bacterium

Wafa Manaf[1], Nageena Dileep[2*], Haifa Manaf[3], Nadiya Dileep[4], Azhar Liyakath[5]

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ABSTRACT

Autism Spectrum Disorder (ASD) is a type of developmental disability which results in social and communication difficulties besides exhibiting stereotyped or repetitive use of objects and bodies. ASD is becoming increasingly prevalent as a significant public health issue, impacting 1 in 100 children globally and showing an apparent increase in cases internationally. Up to 80% of children with ASD experience gastrointestinal (GI) dysfunction, indicating a potential connection between gut microbiota and the development of ASD. This study aims to define the link between gut dysbiosis and ASD and look into the effectiveness of the therapies which use the microbiota, including probiotics, prebiotics, and MTT. A literature review was carried out to identify literature published on Scopus, MEDLINE, and PubMed that focused on paediatric population, and the types of interventions included dietary changes and FMT. Growing evidence for the changed gut microbiota of children with ASD reveals the higher level of *Clostridium* and the lower level of Bifidobacterium population. Supplements of other types of microbes such as probiotics had mixed outcomes in impacting ASD behaviours but positively impacted the gastrointestinal manifestations. The research identifies changes in the gut bacterial makeup of children with ASD, showing increased levels of *Clostridium* and *Sutterella*, which play a significant role in gastrointestinal and behavioral issues. Therapies aimed at the microbiota, such as probiotics and dietary changes, and fecal microbiota transplantation (FMT) demonstrated the ability to enhance symptoms associated with GI issues and ASD.

INTRODUCTION

Autism Spectrum Disorder (ASD) is recognised as a neurodevelopmental disorder, and impairments in interaction, social communication, and the occurrence of repetitive behaviors distinguish it (Namocot, 2023). Gastrointestinal (GI) issues affect up to 80% of children with ASD, suggesting a possible link between gut microbiota as well as ASD development (Yu *et al.*, 2024). ASD affects 1 in 100 children worldwide, and its prevalence remains varied across studies and regions (Chiarotti & Venerosi, 2020). Symptoms often manifest in early childhood but may go undiagnosed until later, and this condition ranges from mild to severe, with some individuals living independently and others requiring lifelong care (Hodges *et al.*, 2020). Conditions such as epilepsy, anxiety, and ADHD often occur alongside autism spectrum disorder; evidence-based psychosocial interventions improve outcomes, but societal support is also critical for accessibility and quality of life (Lai *et al.*, 2020). However, (Fattorusso *et al.*, 2019) study emphasised that children with ASD display imbalances in gut microbiota, which could contribute to both GI and behavioral symptoms.

The gut-brain axis, otherwise referred to as the body's microbiome, was an issue of significant interest due to its potential influence implying the role of the microbiome in ASD. The microbiota comprises trillions of microbes that influence immune response, digestion, and even brain function, with modulation through neural, immune, and metabolic pathways such as antibodies and metabolites, including short-chain fatty acids (Dupont *et al.*, 2020). However, (Iglesias-Vázquez *et al.*, 2020) study explained that a change in gut microbiota may be linked with the emergence and the severity of ASD symptoms including gastrointestinal abnormalities. As a result, it has been established that children with ASD have different bacterial composition in their gut, reduced bacterial diversity and some pathogenic genera according to (Coretti *et al.*, 2018). These imbalances could be beneficial in the conditions of enclave GI problems and anxiety, irritability, and other repetitive behavioral disorders. The treatments that affect such microbiota are the use of probiotics and prebiotics, and dietary management as these help to eliminate these symptoms (Cunningham *et al.*, 2021). The purpose of this study is to determine a connection between functional abnormalities in the gut microbiota and autism signs, as well as to review new findings concerning the gut-brain axis and neurodevelopmental and behavioral changes elicited by an imbalance in the bacterial flora. This work aims at assessing new interventions such as probiotics and diet modulations in children with ASD believed to have an impaired gut brain connection.

[1] Ras Al Khaimah Medical and Health Sciences University, United Arab Emirates
[2] Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates
[3] Neonatology Department, Travancore Medical College, Kollam, Kerala, India
[4] Private Clinic: United Ambulances Services, Abu Dhabi, United Arab Emirates
[5] Department of Pediatrics, GIMS, Greater Noida, Uttar Pradesh, India
[*] Corresponding author's e-mail: nadiyadileep2796@gmail.com

MATERIALS AND METHODS

Research Strategy

A systematic approach was chosen to investigate the link between gut microbiome health and Autism Spectrum Disorders (ASD) in children. An extensive literature search was conducted across various databases, including Scopus, MEDLINE, and PubMed. Key MeSH terms such as "Autism Spectrum Disorder," "Gut Microbiota," "Pediatric Population", "Kids OR "kid", "Child*", "Microbiome Therapy," "Fecal Microbiota Transplant," and "Neurodevelopment "NOT "adults" were used to identify relevant studies. The study combines these primary and secondary keywords using Boolean operators like AND, OR, and NOT.

Inclusion and Exclusion Criteria

In inclusion, articles published in the last 10 years were prioritised to ensure up-to-date findings. However, this study includes papers from the previous two or three decades to cover the maximum amount of research and provide broader research on ASD and gut microbiota. This study only selected peer-reviewed papers and papers published on governmental and federal sites to ensure the authenticity of the research. Inclusion criteria also focused on studies with precise data on gut microbiome and ASD in pediatric populations (children aged 2–18 years). Articles examining interventions such as probiotics, dietary changes, or microbiome transplants were included, provided a control group and quantified both microbial changes and behavioral outcomes in children with ASD. Some research models on animal studies are also evidenced in this paper.

Exclusion criteria include omitted studies with inconclusive findings, those with no control groups, and articles not focused on the gut-brain axis. Those studies involving adults or populations with overlapping conditions like Down syndrome were excluded. The exclusion was justified to maintain focus on children and eliminate unrelated co-morbidities.

Study Selection

The studies were filtered through inclusion and exclusion criteria for relevance and quality of the final research papers selected. Only articles published in the last 10 years were selected to provide a recent understanding of the link between the gut and brain in children with ASD. Earlier and highly influenced studies were incorporated to give background information. Peer-reviewed articles and research extracted from secure official government sources were used to ensure the authenticity of the data collected. Exclude studies did not include control groups, targeted adults only, or reported on related disorders such as Down's syndrome. This may confound results because the review aimed to include only pediatric patients and the gut-brain axis.

Data Analysis

In this research, data analysis was confined to articles published in academic and peer-reviewed journals. Specialists in the subject review scholarly reviewed articles, thus the efficiency of the techniques and recommendations made. Through such articles, this investigation ensures that sorting comprises only the most robust studies on the gut microbiome and ASD in children. Studies include the findings of microbial alteration, behavioral impacts, and effectiveness of the strategies (e.g., probiotics, fecal microbiota transplants) published by peer-reviewed journals. This approach is justified because it gives a better and more accurate account of the constituents of the gut-brain axis in pediatric ASD patients to arrive at definite conclusions (Bozkurt *et al.*, 2019).

RESULT AND DISCUSSION

Gut Dysbiosis in ASD

As mentioned earlier impaired gut microbial called dysbiosis is now linked to ASD (Pulikkan *et al.*, 2019). Many children with ASD have different GI issues, and a disruption of the gut microbiota causes far worse GI and behavioral symptoms. (Navarro *et al.*, 2016), they noted that reduced level of some friendly bacteria (Bifidobacterium) and overgrown pathogenic bacteria (*Clostridia*) have been found commonly described in children with ASD. (Roussin *et al.*, 2020) research indicates that gut dysbiosis plays a critical role in the pathophysiology of ASD. However, studies have identified significant differences in gut microbiota between individuals with ASD and neurotypical controls, revealing an altered bacterial composition that could affect the neurodevelopmental and behavioral characteristics associated with ASD (Fattorusso *et al.*, 2019; Ye *et al.*, 2021). Although *Clostridium* species have been reported at higher levels in individuals with ASD, this genus produces neurotoxins and metabolites that can disrupt the gut-brain axis while contributing to the gastrointestinal and neurological ASD observed symptoms (Fattorusso *et al.*, 2019; Liu *et al.*, 2022). *Clostridia* overgrowth in patients diagnosed with ASD leads to a "leaky gut" through which toxic byproducts infiltrate the bloodstream and thereby affect brain function (Doroszkiewicz *et al.*, 2021). Also, the elevation of *Sutterella*, which exists in children with ASD, can stimulate gastrointestinal inflammation that may influence the neurodevelopment of ASD children and increase ASD symptoms (Bezawada *et al.*, 2020; Doroszkiewicz *et al.*, 2021). The specific role is still under investigation, but *Sutterella* is believed to contribute to inflammation and immune dysregulation factors that are often seen in ASD individuals. However, (Iglesias-Vázquez *et al.*, 2020) illustrated that *Sutterella*'s presence is associated with gastrointestinal disturbances, which are commonly reported in ASD patients and can exacerbate behavioral symptoms. Besides, *Clostridium* and *Sutterella* show imbalances in other bacterial genera such as *Bacteroides* and *Prevotella*. These bacteria are associated with maintaining gut homeostasis and supporting immune function.

Further, the study by (Strati *et al.*, 2017) demonstrates considerable shifts in gut microbiota and microbiota in subjects of severe ASD with elevated *Firmicutes/ Bacteroidetes* ratios and particular bacterial disruptions. A reduction in their levels in individuals with ASD may contribute to dysregulation of gut immunity and exacerbate systemic inflammation. In the review, (Hughes *et al.*, 2018) study suggested that changes in the gut microbial composition could impact ASD and neuro more than development and behavior. These findings show potential for gut-targeted therapies such as probiotics and dietary interventions to alleviate some symptoms of ASD by addressing the underlying dysbiosis, so the connection between gut health and ASD is represented as a critical area of ongoing research (De Sales-Millán *et al.*, 2023; Liu *et al.*, 2022).

Variation of Gut Bacterial Composition between Patients with ASD and Neurotypical Individuals

Individuals with ASD show distinct variations of gut bacterial composition compared to neurotypical individuals. In individuals with ASD, *Firmicutes* make up approximately 60.9% of the gut microbiota, while *Bacteroidota* accounts for 17.1%, *Actinobacteriota* for 15.4%, and *Proteobacteria* for 4% (De Sales-Millán *et al.*, 2024). Conversely, neurotypical individuals have different profiles, with *Firmicutes* at 59.6%, *Bacteroidota* at 15.1%, *Actinobacteriota* at 17.2%, and *Proteobacteria* at 3.6%. Notably, *Blautia* levels are significantly lower in individuals with ASD (3.46%) compared to neurotypical individuals (9.80%) as shown in Table 1, while *Prevotella* is more abundant in those with ASD (2.54% vs. 0.71%). Other differences in genus level include variations in *Clostridium* species, with ASD individuals having higher levels of *Clostridium_XI* but lower levels of *Clostridium_ XVIII*. However, the study by (De Sales-Millán *et al.*, 2024) focused that *Megamonas* appear uniquely present in females with ASD but are absent in both neurotypical groups, and these compositional differences in gut bacteria suggest potential links between microbiome diversity and ASD. In addition to the noted differences in *Bacteroidetes* and *Firmicutes*, individuals with ASD have shown higher proportions of other bacteria and increased *Clostridium* species (Table 1). Patients diagnosed with ASD present changes in microbiota in the gastrointestinal tract with increased presence of such bacteria as *Clostridium*, *Desulfovibrio*, and *Sutterella*. (Hughes *et al.*, 2018) results showed that carcinogenic sulfur compounds formation by *Desulfovibrio* might affect gut microbiota composition, contributing to dysbiosis and elevated *Sutterella* concentration, which is associated with gut inflammation exacerbation and ASD manifestation.

Table 1: Gut Microbiota Genera Involved in Autism Spectrum Disorder (ASD), Characteristics, Classification, and Functional Role in ASD Development (Bezawada *et al.*, 2020)

Genus	Characteristics	Bacterial Classification	Function in ASD Development
Bacteroides	Gram-negative, anaerobic, non-spore-forming	*Bacteroidetes*	Levels observed to be higher As compared to children diagnosed with ASD. It also plays a role in breaking down complex carbohydrates though it forms neurotoxic metabolites that interfere with communication between the gut and the brain which can alter gastrointestinal and behavioral conditions (Coretti *et al.*, 2018).
Clostridium	Gram-positive, anaerobic, spore-forming	*Firmicutes*	Probiotic imbalance; overgrowth of specific bacteria such as *Clostridium* bolteae identified as associated with ASD. These include neurotoxins like propionic acids that might interfere with signals within the brain leading to behavioral disorders and oversupply of antibiotics (Rose *et al.*, 2018).
Prevotella	Gram-negative, anaerobic, non-spore-forming	*Bacteroidetes*	The AChE levels were reduced in the present study in comparison to the control in the ASD group. SCFAs are also produced by fiber that it is believed to enhance the health of the gastrointestinal tract. Their deficiency might also adversely affect gut structural components and increase the inflammatory response (Strati *et al.*, 2017).
Bifidobacterium	Gram-positive, anaerobic, non-motile	*Actinobacteria*	Involved in regulation of immune response and also in the regulation of intestinal permeability. Its lack may cause elevated gut permeability leading to the appearance of "leaky gut" wherein toxic by-products are allowed entry into circulation, as well as hinder brain development (Berding & Donovan, 2018).

Lactobacillus	Gram-positive, facultative anaerobe	*Firmicutes*	Used less in ASD but is recognised for its capability to produce lactic acid, to regulate Gut pH and to support healthy gut. A deficiency may lead to dysbiosis and impaired COM obtained communication affecting their neurodevelopment, and behavior (Pulikkan *et al.*, 2018).
Desulfovibrio	Gram-negative, sulfate-reducing bacteria (SRB)	*Proteobacteria*	*Desulfovibrio* is increased in ASD and it forms hydrogen sulfide which is known to be toxic to the epithelial cells of the gut leading to inflammation and a leaky gut. Dysbiosis may lead to increased permeability of the gut wall and permit neurotoxic metabolites to enter the brain and modulate ASN symptomology (Tomova *et al.*, 2015).
Parabacteroides	Gram-negative, anaerobic, non-spore-forming	*Bacteroidetes*	It is increased in some persons with ASD and influences neurotransmission and inflammation. They are connected with higher immune activation and neuroinflammation that lead to ASD symptoms (Garcia-Gutierrez *et al.*, 2020).
Collinsella	Gram-positive, anaerobic, non-spore-forming	*Actinobacteria*	It has a break down role for the aspect of complex carbohydrates and has a responsibility in the aspect of gut health in ASD. Its decrease probably affects both metabolic and immune processes, likely being involved in the gastrointestinal disorder which is manifested in most children suffering from ASD (Srikantha & Mohajeri, 2019).
Sutterella	Gram-negative, anaerobic, non-spore-forming	*Proteobacteria*	Increased rate of ASD with inflammation and gastrointestinal abnormalities. If so, its increase might be associated with changes in gut integrity and immune regulation, which clearly affects ASD development (Hiippala *et al.*, 2016).

Brain Axis Influence on ASD

The gut microbiome plays an important role in brain formation because it is associated with neurological disorders and with communication between the CNS and the macrobiotics through immune, neurotransmitter, and hormonal pathways (Suganya & Koo, 2020). Microbial metabolites like SCFAs or short-chain fatty acids modulate gut immunity and reinforce the intestinal barrier, which prevents harmful pathogen invasion that triggers neuroinflammation in conditions like autism spectrum disorder (ASD) as mention in Table 2. Doroszkiewicz *et al.* (2021) study analysed that dysbiosis can cause gut permeability (leaky gut), allowing harmful bacteria into circulation and aggravating neurodevelopmental issues. However, the Gut microbiome also affects the migration of immune cells like IFNγ+ NK cells and IgA+ plasma cells to the CNS, regulating neuroinflammation and guarding the developing brain against infections (Moradi *et al.*, 2021). Under certain conditions, cells migrate and induce inflammation, demonstrating gut microbiota's dual role in maintaining CNS homeostasis or contributing to neurodevelopmental disorders like ASD, and its balance depends on it (Table 2). According to (Azhari *et al.*, 2019), gut microbiotas have a profound role in neurodevelopment through cell wall components and systemic cytokine regulation.

Derived from bacterial cell walls, peptidoglycan can cross the blood-brain barrier and activate pattern recognition receptors (PRRs) in the brain, and this activation influences synaptogenesis in areas such as the prefrontal cortex and cerebellum, which are crucial for social behavior and stress responses linked to autism spectrum disorders (Oummadi, 2023). In addition to peptidoglycan, cytokines are circulating to the CNS; these molecules impact processes like neurogenesis, glycogenesis, and neuronal migration while making them critical to neurodevelopmental disorders (NDDs) (Wang *et al.*, 2023). Maternal immune activation (MIA) has garnered attention for the association of inflammatory cytokines such as IL-16 and IL-6 with increased risk for NDDs in offspring (Bergdolt & Dunaevsky, 2019). In pregnant females, if IL-6 is elevated, it will further boost IL-17 production while directly affecting neurons through synaptogenesis, which will disrupt hippocampal connectivity (Mohebalizadeh *et al.*, 2023; Wang *et al.*, 2023)) analysed that microglia are resident immune cells of the brain that play a pivotal role in modulating neurodevelopment by pruning synapses, regulating neural progenitor cells, and influencing myelination. However, (Otero & Antonson, 2022) emphasised that disruptions in microglial functions, including their synaptic pruning activity via the complement system, are linked to NDDs, as gut microbiota impacts microglial maturation and function with microbial metabolites such as SCFAs.

Furthermore, microbial-derived aryl hydrocarbon receptor (AHR) agonists also control microglial synthesis of anti-inflammatory factors TGFα and cerebrovascular endothelial growth factor VEGF-B amplifying the relationship between gut microbiota and brain inflammation (Wang *et al.*, 2023). It generates a variety of neurotransmitters that shape brain activity, such as serotonin and dopamine, which are among

these metabolites (Table 2). However, there are two metabolites, taurine and 5-amino valeric acid, that help enhance social activity and reduce stereotypic movements in an ASD model. The gut microbiota also affects the hypothalamic-pituitary-adrenal (HPA) axis, the hormones of which get deleteriously altered in a context that can cause increased stress hormone cortisol, which is seen in individuals with ASD (Rusch *et al.*, 2023). However, some bacterial strains can reduce social stress by normalising glucocorticoid concentrations. These findings illuminate vast bidirectional communication between the Brain and gut with modulation into the Vogus nerve.

ASD is marked by deficits in social interaction and communication and varying degrees of repetitive behavior. It is also associated with genetic and environmental factors. (Borrego-Ruiz & Borrego, 2024) identified different genes related to ASD through large-scale genetic analyses, and yet, it is important to consider infections, diet, and toxicity. Recent focus has been devoted to relationships between GI dysfunction in ASD and dysbiosis as research has revealed variations in microbial profiles in children with ASD compared to TD in Table 2. One notable example is the elevated presence of Clostridioides genus in ASD individuals. The research illustrated that microbial metabolites like 4-EP(S) and p-Cresol sulfate are derived from aromatic amino acids and have been implicated in processes like neuroinflammation. Further elaborated by (Zheng *et al.*, 2021), serotonin dysregulation observed in ASD also points to gut-brain interactions with research emphasising the abnormal metabolism of tryptophan in autistic individuals.

A range of therapeutic approaches for the microbiota-gut-brain axis encompassing prebiotics, probiotics, and fecal microbiota transplantation (FMT) has shown potential. Probiotics like *Lactobacillus reuteri* and *Bacteroides* fragilis have confirmed improvements in ASD-related behaviors and gut permeability in murine models (Wang *et al.*, 2023). As shown in Table 2, FMT restores microbial diversity and improves GI and behavioural symptoms in small-scale clinical studies, but factors like donor-recipient compatibility and administration methods remain critical challenges for FMT. Alterations in microbial composition, such as increased *Bifidobacterium* and *Bacteroidaceae* and reduced abundance of certain taxa, have been associated with ADHD symptoms. However, (Song *et al.*, 2022) elaborated that transplanting ADHD-associated microbiota into mice led to ADHD-like behaviors that point out potential causal gut-brain axis roles. Probiotics and omega-3 polyunsaturated fatty acids (PUFAs) confirmed therapeutic promise in ADHD by modulating the immune response and intestinal barrier stability (Table 2). For instance, Rett Syndrome (RTT) is a severe NDD that predominantly affects females and has also been linked to gut microbiota alterations. These RTT patients show reduced microbial diversity in taxa like *Bifidobacterium* and *Lactobacillus* (Borghi & Vignoli, 2019). These findings have revealed a significant attendance of FMT to improve microbial imbalance and gastrointestinal and behavioral manifestations of ASD. Also, gut dysbiosis observed in ADHD children, including increased Bifidobacterium count, has been associated with ADHD symptoms, suggesting a causal connection of the gut-brain axis in neurodevelopmental disorders, including Rett Syndrome.

Table 2: Mechanisms Linking Gut Microbiota to Autism Spectrum Disorder (ASD) Development

Mechanism	**Gut Microbes Involved**	**Effect on ASD Development**	**Pathophysiological Impact**
Gut-Brain Axis Disruption	*Clostridium*, *Bacteroides*	Microbes produce neurotoxic metabolites (e.g., propionic acid) that can alter brain function and behavior.	Disruption in neurotransmission, increased production of neuroactive compounds, and imbalanced synaptic activity contribute to abnormal behaviors and cognitive dysfunction in ASD (Coretti *et al.*, 2018).
Altered Immune Response	*Desulfovibrio*, *Sutterella*	Dysbiosis triggers chronic gut inflammation, which activates systemic immune responses and neuroinflammation.	Heightened inflammatory responses in the gut increase pro-inflammatory cytokines like IL-6 and TNF-α, promoting neuroinflammation and neural circuit disruptions involved in ASD (Kang *et al.*, 2017).
Leaky Gut and Gut Permeability	*Bifidobacterium*, *Lactobacillus*	Reduced beneficial bacteria compromise gut barrier integrity, increasing permeability ("leaky gut").	Toxins and bacterial metabolites enter the bloodstream, potentially crossing the blood-brain barrier, impacting neurodevelopment, and increasing ASD symptom severity, including GI disturbances (Berding & Donovan, 2018)
Short-Chain Fatty Acid (SCFA) Deficiency	*Prevotella*, *Bifidobacterium*	Reduced SCFA production affects gut health, immune balance, and neurotransmitter synthesis, all crucial for brain health.	SCFAs regulate immune responses and maintain gut epithelial integrity. Reduced levels lead to increased inflammation, impair brain development, and affect signaling pathways linked to ASD (Coretti *et al.*, 2018).

Neurotransmitter Dysregulation	*Bacteroides*, *Clostridium*	Gut microbiota modulates serotonin, dopamine, and GABA levels, crucial for regulating mood and behavior.	Imbalances in neurotransmitter production linked to the altered microbial composition may contribute to ASD-related behaviors like anxiety, repetitive behaviors, and social impairments (Strati *et al.*, 2017).
Oxidative Stress	*Desulfovibrio*, *Clostridium*	Overgrowth of certain microbes increases oxidative stress markers, exacerbating brain inflammation and damage.	Increased oxidative stress in the gut and brain leads to mitochondrial dysfunction and neuronal damage, which is commonly observed in individuals with ASD, worsening cognitive and behavioral symptoms (Dargenio *et al.*, 2023).

Contribution of Gut Microbiota in the Development of ASD

The gut microbiota's potential contribution to the development of (ASD) has gained attention for its association between gastrointestinal disturbances and neurodevelopmental disorders. (Yu *et al.*, 2024) research emphasised that children with ASD have distinct gut microbiota composition compared to neurotypical individuals, bacterial taxa being differentially abundant, and there are disruptions in the gut-brain axis. However, (ERSÖZ ALAN & Gülerman, 2019)finding highlighted that individuals with ASD tend to have fewer beneficial bacteria such as *Bifidobacterium* and *Collinsella*, which belong to the *Actinobacteria* Phylum. On the other hand, higher abundance levels of *Proteobacteria* have been reported, particularly from the family of Enterobacteriaceae, which are considered to foster inflammation in the gut in individuals with ASD (Gomaa, 2020). Other bacterial taxa observed in disproportionately high amounts are Prevotellaceae and *Parabacteroides* from the *Bacteroidota*, which may be associated with gastrointestinal complaints that most ASD patients exhibit (Peralta-Marzal *et al.*, 2024). These outcomes stress that microbial dysbiosis may play a role in ASD pathogenesis, and modulating microbial ecology, including by use of probiotics or fecal microbiota transfer, may provide one of the reasons for ameliorating gastrointestinal and behavioural manifestations in children with ASD. However, (Peralta-Marzal *et al.*, 2024) research shows that gut microbiota is crucial for the bidirectional gut-brain axis, especially in patients diagnosed with ASD. Some of these mechanisms include modulation of immune responses, generation of neuroactive metabolites, and effects on the barrier in the gut. Moreover, the presence of particular microbial genera in ASD individuals, including a reduced amount of *Bifidobacterium* and *Collinsella* and increased Prevotellaceae and *Parabacteroides* that, are thought to affect neurological signaling (Berding & Donovan, 2018). This communication between the gut and brain is believed to affect behavior, thinking, and even feelings. Although, (Chernikova *et al.*, 2021) study highlighted the alteration of gut microbiota by probiotics or fecal microbiota transplantation can be therapeutic targets for AS-designated gastrointestinal and neurological manifestations of ASD.

Dietary Interventions

Parents of children with ASD often favor gluten- and casein-free diets (GFCF), grounded in the belief that certain peptides from these foods might worsen symptoms. The Gluten-Free Casein-Free (GFCF) diet has been investigated as a potential treatment for (ASD) because of the possible connections between gluten, casein, and brain function (Christison & Ivany, 2006). However, the study by (Knivsberg *et al.*, 2003) suggested that eliminating casein and gluten could reduce autism-like symptoms by preventing the formation of opioid-like peptides from these proteins which may cross intestinal and blood-brain barriers. Studies like (Knivsberg *et al.*, 2003) reported reduced autistic behaviors following the GFCF diet, while others, like (Elder *et al.*, 2006) identified no significant behavioral improvements after 6 weeks on a diet. Further, (Mari-Bauset *et al.*, 2014) study demonstrated that parents observed reductions in gastrointestinal symptoms and repetitive behaviors in their children on the GFCF diet. (Whiteley *et al.*, 2010) argued that longer durations of 6 months or more may be necessary to see effects, though this remains contested. However, (Başpinar & Yardimci, 2020) study supported that elimination diets should be considered only when there's a known intolerance to gluten or casein. It indicates that a low GFCF diet might lessen autism-like behaviors in certain children; other research has shown only mild effects. Long-term beneficial results, especially in regard to digestion and compulsive behaviors might be observed; however, elimination diets should only be attempted if certain pathologies involving intolerances are confirmed.

Probiotics

Probiotic strains such as *Lactobacillus* and *Bifidobacterium*, are proposed to balance gut microbiota in individuals with ASD (Sanlier & Kocabas, 2023). (Sivamaruthi *et al.*, 2020)study randomised controlled trial (RCT) proposed that probiotics improved GI symptoms and marginally enhanced social responsiveness in ASD patients but the overall impact on core ASD behaviors remains inconsistent. (Patel *et al.*, 2022)review emphasised that probiotics and gut microbiota in children with (ASD) has produced mixed findings. According to (Buffington

et al., 2016)research, animal studies demonstrated that probiotic supplementation could improve ASD-like symptoms and social behavior in mice, but human studies are less conclusive. A meta-analysis by (He *et al.*, 2023) investigated the effect of probiotics such as *Lactobacillus plantarum* and *Bifidobacterium longum* on ASD symptoms. Probiotics did help alleviate gastrointestinal (GI) symptoms in other research, and multi-strain probiotics such as blends containing *Lactobacillus reuteri* appeared to show better outcomes than single strains in improving behavior in children with ASD (Buffington *et al.*, 2016; Wang *et al.*, 2023). Despite these promising insights, (He *et al.*, 2023)suggested that high-quality clinical trials are still required to substantiate probiotics' therapeutic impact on ASD-related behavioral symptoms. The findings from the current literature review indicate that only a few clinical trials on the effects of probiotics on people with ASD are published. Those studies demonstrate improvements in gastrointestinal symptoms when using probiotics and multi-strain blends but cannot conclude consistent benefits on the core ASD symptoms.

Microbiota Transfer Therapy (MTT)

MTT refers to transplantation to the subjects with ASD of a microbiota sourced from healthy individuals for its normalising impact on the gut. A study conducted by (Kang *et al.*, 2017) illustrated that Microbiota Transfer Therapy (MTT) demonstrated there was a notable enhancement in gastrointestinal (GI) symptoms as well as autism symptoms among children with ASD. After a treatment regimen that included antibiotics bowel cleanses, and fecal microbiota transplants (FMT), included participants experienced an 80% reduction in GI symptoms like constipation and diarrhea, and behavioral improvements in ASD symptoms were also observed and both GI and ASD improvements persisted 8 weeks post-treatment (Tan *et al.*, 2021). Increased microbial diversity including abundance of beneficial bacteria like *Bifidobacterium* and *Prevotella* was also noted by (Adams *et al.*, 2019; Kang *et al.*, 2019) study also demonstrated promising results in children with ASD after MTT a procedure involving the transfer of a healthy donor's fecal microbiota to the patient and an open-label study showed that after two years, 45% of children saw a reduction in core ASD symptoms by 50% while their GI symptoms improved by 58%. Further, (Kang *et al.*, 2019) analysed that long-term follow-up shows intervention had sustained effects with changes in microbial diversity resembling that of neurotypical individuals. Nevertheless, the lack of control groups in some MTT studies may limit the robustness of these findings to some extent.

Microbiota Transfer and Other Therapies in ASD

ASD has prompted microbiota transfer therapy (MTT) and other gut-targeted interventions including use of probiotics and changes in diet (Adams *et al.*, 2019). (Kang *et al.*, 2019)research exploring the gut-brain axis in ASD has shown interest in microbiota transfer therapy (MTT), probiotics, and dietary interventions. However, (Kang *et al.*, 2017) suggested that gut microbiota influence ASD symptoms by altering the gut-brain axis through several mechanisms for instance, microbial imbalances cause increased gut permeability allowing inflammatory molecules to reach the brain, which affects neural pathways tied to behavior. Also, (Taniya *et al.*, 2022) study elaborated that microbes may also produce neuroactive compounds like serotonin or GABA impacting social behavior and repetitive actions and these imbalances can disrupt digestion leading to gastrointestinal disturbances commonly seen in ASD.

Discussion

The discussion emphasised the microbiota in relation to ASD has attracted much interest with different studies indicating the role of gut bacteria in the development of the brain and behaviour. The exact mechanisms and clinical relevance of these findings are not yet cleared and are calling for a more critical evaluation of current evidence. Navya (Bezawada *et al.*, 2020) study elaborated that ASD children are seen frequently exhibit altered gut microbiota characterised by an increase in certain bacteria like *Clostridium* and *Sutterella* and a reduction in beneficial species such as *Prevotella*. However, one major limitation in current research is heterogeneity in methodologies like inconsistent use of controls varying diagnostic criteria for ASD and differences in sample collection and sequencing techniques. Without controlling for these factors, there is a gap to conclude that microbial differences are intrinsically linked to ASD. Although, (Loth *et al.*, 2016) study conducted on the link between autism spectrums disorder (ASD) and gut microbiota as the scientific community aims to use this association for identification. Lacking precisely validated gut-based biomarkers diagnosing ASD, several arising methodologies exist.

However, (Ye *et al.*, 2021) study identified that there is a low concentration of better bacteria, especially Bifidobacterium, and a higher chance of pathology. Apart from traditional stool analysis, modern techniques are available such as Metagenomic sequencing to determine the gene content of these microbes, which assists in establishing a direct relationship between particular microbes and ASD. (Eicher & Mohajeri, 2022) study approach focuses on microbial metabolites being the chemical output of these bacteria, some of which are likely to be shifted in autistic patients. To model the risk of ASD based on gut microbiome data, active machine learning algorithms are being trained and will soon be available; these methods are relatively new in diagnosing, giving hope for the future of diagnosing persons with ASD. However, (Zou *et al.*, 2020) study illustrated that the mechanisms by which the gut-brain axis influences these CNS functions via short-chain fatty acids, neurotransmitters, and the immune system or which guts dysbiosis affect the core signs of ASD. Although, as per (Oh & Cheon, 2020) research, propionic acid, a short-chain fatty acid synthesised by some gut bacteria has been

found to cause ASD-like behaviors in animal models, but direct extrapolation to humans is difficult due to the complexity of neurodevelopment and many genetic factors underlying ASD. Some gut pathologies arising from microbiota imbalance, including the overgrowth of *Clostridium* and *Desulfovibrio*, produce neurological toxins, including propionic acid, which interferes with neurotransmission and may help explain behaviors seen in ASD (Coretti *et al.*, 2018). MacFabe (2015) argued that the disintegration of the communication between the gut and the brain, combined with the increase of the permeability of the intestinal barrier leads to the introduction of toxins from the bloodstream into the brain. However, Liwinski and Elinav (2020) noted that causality of microbiota for the development of ASD remains ambiguous since, according to many investigations, they show only coexistence. Despite the positive outcomes observed from the clinical studies, variability in the results obtained across the human trials has necessitated more rigorous research using better-quality interventions.

Furthermore, it is still doubtful whether microbiota-targeted interventions such as prebiotics, probiotics, or fecal microbiota transplantation can be used as therapeutic options. The study by Settanni *et al.* (2021) highlighted significant reductions in gastrointestinal and behavioral symptoms, but the durability and safety of these treatment procedures are questionable. The possibility of the placebo effect, small sample sizes, and the absence of keen, controlled trials hampers these findings. Further, Liwinski and Elinav (2020) study examined the therapeutic efficacy of targeting gut microbiota in ASD and answered whether such interventions can be anything more than treatment of symptom(s). Zhu *et al.* (2022) study suggested that ABA and OT are identified as evidence-based for enhancing functional and adaptive communication, daily living, and social, and motor development. Other dietary interventions, such as omega-3 fatty acids, benefit behavior, though these findings are inconclusive. In addition, Awaad (2022) study discussed that sensory integration therapy (SIT) is useful for helping children with sensory processing, hyperbaric oxygen therapy (HBOT) and acupuncture give limited assistance. Anxiety can be controlled and treated with Cognitive Behavioral Therapy also known as CBT for people with higher intellectual capacity. This study identified that more and more interest has been gain to the gut- brain axis and its relationship to ASD, the specific processes are not yet well understood. Literature shows that gut–brain axis contributes to neurodevelopment and behaviour but there is a limit focus on the quality of research. Compared with antibiotics, antibiotic-associated microbiota-targeted therapies such as probiotics and fecal microbiota transplantation provide evidence of efficacy but their effect and safety in the long-term are abilities more research. If the patient's problem is severe enough, dietary and behavioral practices, together with medical treatments, can be the most effective ASD intervention.

CONCLUSION

It can be concluded that the increasing fascination with the gut-brain connection is a potential contributor to changes in ASD symptoms. A substantial body of evidence suggests gut dysbiosis has a significant role in both behavioral and gastrointestinal symptoms among children with ASD. While microbiota-targeted interventions such as fecal microbiota transplantation or probiotics show therapeutic promise, several critical questions remain unanswered regarding their safety, effectiveness, mechanisms of action, and the longevity of their effects. The research emphasises that there is a pressing need for further extensive studies to develop individualised reproducible microbiota-based therapies, considering the wide variability of symptoms among ASD patients. The review further emphasises the need to apply microbial health findings to managing ASD. It suggests the need for larger clinical trials to establish microbiota and neurodevelopmental disorders such as ASD.

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