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REVIEW ARTICLE

Elucidating the interplay between gut microbiota and autism spectrum disorder. New insights and therapeutic perspectives

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ABSTRACT

Autism is a complex neurodevelopmental disorder characterized by a wide range of cognitive, behavioural and communication impairments. Children with autism have a distinctive and underdeveloped range and volume of gut bacteria (microbiome) which is often not related to their diet. Evidence gathered throughout years of research suggests that the pathway between gut bacteria and the central nervous system, referred to as the gut-brain axis (GBA), has a profound effect on the social behaviours of autistic children. The gut microbiome has been shown to play a vital role in the manifestation of autism spectrum disorder (ASD) symptoms as gut dysbiosis - an imbalance in the gut microbiome - affects brain development through processes regulated by the neuroendocrine, neuroimmune and autonomic nervous systems. Although dysregulation of the gut microbiome and subsequent disruption of GBA are thought to contribute to the pathogenesis of autism, the underlying mechanisms and the extent to which the microbiome contributes to neurodevelopmental disorders remain unclear. In this review, we focus on understanding the complex and multidirectional interplay between gut microbiota and ASD based on evidence mounted over the years. Furthermore, we examine how genomics, metabolomics and microbiome components can be integrated to unravel this multifactorial disorder. The ability to understand the underlying mechanisms involved in ASD will pave the way for future advancements in therapy and treatment.

KEYWORDS

autism, gut microbiome, gut-brain axis

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex group of neurodevelopmental conditions characterized by a wide range of impairments including altered social communication and interaction as well as the presence of restricted, repetitive patterns of behavior, interests, or activities.

The prevalence of ASD in children and adolescents has been increasing in recent years, with latest estimates showing that approximately 2% (from 1% to 3%) of children in the United States being diagnosed with ASD [1, 2]. These variations in the diagnosis of ASD are attributed to geographical, socioeconomic, and methodological factors [3–5], with socio-economic factors being central in the detection and diagnosis of ASD [4]. In terms of gender, males are affected more frequently than females by the condition [6]. Although ASD has been well defined in terms of behavioural diagnosis, what causes ASD still remains a mystery. What has been well understood from extensive research to date is that the etiology of ASD is

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multifactorial involving a complex interplay of genetic and environmental factors that contribute to its manifestation [7–9]. To add to the complexity of the multifaceted nature of ASD, the gut microbiome has been drawing researcher's attention in the last decade regarding its role in the development and etiopathogenesis of ASD. Mounting evidence to date highlights the complexity of ASD with the involvement of the gut microbiome, further suggesting a bidirectional communication between the central nervous system and the gastrointestinal tract, known as the microbiota-gut-brain axis [10–12].

GENETIC AND ENVIRONMENTAL FACTORS CONTRIBUTING TO ASD

Extensive genetic research has highlighted the importance of genetic factors in the development of autism. These include, copy number variations, rare common variants and de novo mutation underlying ASD etiology [13].

Genome-wide association (GWAS) and genetic studies have identified common genetic variants; mainly single nucleotide polymorphisms (SNPs), to be associated with autism [14–16]. In ASD cases, SNPs collectively account for a substantial proportion (estimated at 40–60%) to be of heritable risk [17, 18]. Multiple investigations using large-scale sample sizes have demonstrated that the cumulative burden of these common variants contributes to ASD susceptibility, even though the effect sizes of individual loci remain modest. It remains unclear still how common variants interact and aggregate to increase disease liability [17, 18]. The presence of SNPs in various genes, including those involved in synaptic function, has been associated with increased risk for developing autism [19, 20].

Large-scale meta-analyses have been particularly pivotal in identifying risk loci at genome-wide significance levels. One of the latest meta-analysis conducted, involved over 18,000 ASD cases and almost 28,000 controls, culminating in the identification of five genome-wide significant loci [16]. In another similar study, novel candidate genes such as DDHD2 were found to be implicated in the etiology of ASD [21], underscoring the value of large, genetically informative cohorts in uncovering the subtle contributions of common variants. These studies illustrate that common genetic variation, while individually modest in effect, collectively contributes essential information about the biological mechanisms underlying ASD.

The heritability component linked to ASD can be further demonstrated in twin studies with heritability estimates as high as 0.9 in twin studies [22]. Siblings of individuals with ASD are at a substantially higher risk, being approximately 25 times more likely to be diagnosed compared to the general population [22].

Apart from the heritability component, a number of large-scale whole-exome sequencing studies have demonstrated that rare de novo single nucleotide variants (SNVs) and copy number variations (CNVs) occur at a higher rate in ASD probands compared to unaffected siblings, supporting a strong link between these mutations and autism risk [23–25]. In these studies, de novo loss-of-function and missense mutations in genes with critical roles in synaptic formation and neuronal development have been identified repeatedly in affected individuals, highlighting their importance in neurodevelopment [25, 26].

Additionally, the co-occurrence of multiple extreme de novo variants in affected individuals compared to controls is more prevalent, as well as in patients with ASD who had significantly lower IQs [27]. This suggests that the cumulative effect of multiple rare variants may exacerbate disease severity [25]. Studies have shown that approximately 49 genes show higher frequencies of disruptive de novo variants in individuals ascertained to have severe neurodevelopmental delay, whereas 53 show higher frequencies in individuals ascertained to have ASD [28]. Furthermore, the observed difference in the rate of de novo mutations between males and females with ASD may be explained either by a protective effect conferred by genetic factors in females or by an ascertainment bias, whereby affected females tend to exhibit more severe phenotypes compared to affected males [29].

Although a number of neurodevelopmental genetic disorders such as epilepsy, obsessive compulsive disorder (OCD) and Angelman syndrome (AS) co-occur with ASD [30–32], single gene mutations and copy number variations do not add up to the majority of ASD cases. In fact, when found, genetic alterations are usually de novo rather than inherited [33]. It has become apparent that polygenetic influences underly the etiology of ASD whereby changes in multiple genes might add up to a threshold that disrupts cellular pathways [34]. A selected overview of major genetic findings associated with ASD and their prevalence in ASD patients is summarized (Table 1). Despite the strong contribution of genetics to ASD, it is clear that genes alone cannot account for all cases. It is now well established that environmental factors play a crucial role in modulating the risk of developing ASD through their interactions with various genes [35]. Some of these environmental factors that are associated with an increased risk of ASD include prenatal exposure to infections, maternal immune activation, exposure to certain medications during pregnancy, and exposure to environmental toxins [36]. Exposure to environmental toxicants during prenatal development may impact brain development, thus altering cognitive, social, and motor skills [37]. Prenatal exposure to thalidomide and valproic acid has been shown to elevate ASD risk, while supplementation with folic acid during pregnancy may mitigate risk in patients exposed to antiepileptic drugs [38].

In addition, advanced parental age, assisted reproductive technologies, nutritional factors, pre-mentioned maternal infections and diseases, environmental chemicals and toxicants, and medications, as well as other conditions have also been described as high-risk for developing ASD [39]. The environment encompasses a broad range of non-genetic factors, spanning from viruses to medications and from chemical or physical agents to social and cultural influences [40]. It is therefore important not to focus on the "genes of autism," which implies determinism, but to study instead the

Table 1. Summary of evidence for selected ASD candidate genes (and/or regions), their association with ASD and their prevalence/effect size across ASD patients

Genetic Type/Gene or Region	Association with ASD	Estimated Prevalence/Effect Size	Reference(s)
Twin studies (heritability)	Monozygotic concordance rate significantly higher than dizygotic twins	Heritability estimates range from ~64% to 91%.	[22, 44–53]
Rare de novo protein truncating variants (PTVs)/SNVs	High-impact variants disrupting gene function	Found in ~8%–10% of ASD probands and are rare in unaffected individuals.	[28, 48, 51, 53–56]
Copy-number variants (CNVs) (e.g. 16p11.2 deletion/duplication, 15q11-q13 duplication, 22q11.2 deletion)	Sensory and synaptic deficits; strong ASD risk	CNVs in ~10–20% of ASD cases; specific CNV syndromes in ~1%.	[46, 48, 53, 57–60]
Dup15q syndrome (15q11.2-q13.1 duplication)	Most common known genetic cause of syndromic ASD; associated epilepsy, intellectual disability	Accounts for ~1–3% of all ASD cases.	[61–64]
PTEN mutations	Associated with macrocephaly, synaptic overgrowth and ASD	Occur in ~2% of all ASD cases, estimated to be higher (~20%) in individuals with ASD and macrocephaly.	[48, 65–67]
Synaptic genes: SHANK3, neuroligins (NLGN3/4), neurexins	Affect synaptic formation and signalling; disruption linked to ASD.	Rare mutations, high-effect in subgroups.	[51, 68–75]
High-confidence ASD-associated genes: ASH1L, CHD8, MECP2	Implicated in chromatin regulation, gene expression, neuronal development	Rare variants with pleiotropic effects (epilepsy, ADHD, ID).	[48, 76–80]
Common SNPs in genes: CNTNAP2, MTHFR, OXTR, VDR	Modest associations, varied by allele	Identified significant ORs for select SNPs in meta-analysis.	[50, 81, 82]
Polygenic effects (GWAS-identified loci)	Many small-effect variants cumulatively contribute risk	May explain ~10–12% of ASD risk variance.	[47, 83–85]
X-linked genes DDX53 (and PTCHD1-AS)	Maternally- inherited variants in the DDX53 gene are linked to ASD.	~0.04%–0.05% of ASD patients in this study were found to carry rare DDX53 variants	[86–88]

effects of the genome integrated with environmental, epigenetic, or genetic contributions [41]. Recent studies suggest that approximately 50% of ASD cases can be attributed to environmental factors [42]. These environmental factors, including prenatal conditions, have a pivotal role in the early stages of autism development, although the precise mechanisms remain largely undefined [40, 43]. Although their potential roles in ASD etiology have been investigated, the exact mechanisms of how these factors contribute to ASD are not clearly understood.

THE GUT-BRAIN AXIS IN AUTISM: EXPLORING THE ROLE OF THE MICROBIOME

A mounting body of evidence has linked the gut microbiota to the multifaceted nature of ASD (Table 2). The microbiota is considered a non-genetic, yet heritable [89] contributor to psychiatric behaviours. These microbial communities consist of microorganisms residing in the gastrointestinal (GI) tract from where they affect development and function of the immune, metabolic and nervous systems [90, 91]. The influence of gut microbiota on autism is complex and multifactorial, involving interactions between genetics, the environment, and the immune system [8, 40].

Dietary components, particularly proteins and their metabolites, have been shown to significantly affect the microbiome composition and alter its function, either within a host or when inherited by its offspring [92]. It has been reported that specific microbial phyla, such as *Bacteroides* and *Firmicutes*, are sensitive to dietary proteins, which can lead to alterations in microbial diversity and functionality [93]. In fact, dietary changes may also modify disease symptoms in individuals, when coupled with a genetic risk [94, 95]. On the other hand, a "pathogenic" microbiome itself can trigger systemic inflammation, metabolic disorders, and/or alterations in neurotransmitter metabolism, all of which can further result in neurodevelopmental disorders in otherwise non-predisposed individuals [96, 97]. For example, transplant of microbiota from patients with ASD into germ-free mice induces ASD-like behaviours in these animals, suggesting that the microbiome alterations can lead to changes in behaviours typical to ASD, especially social deficits [96, 98].

Dysbiosis in the gut microbiota, characterized by an imbalance in the composition and function of gut microbial communities, has been increasingly recognized as a potential contributing factor to ASD [99]. It is hypothesized that alterations in the gut microbiota can impact brain development and function through various mechanisms, including

Table 2. Major research findings linking the gut microbiota with ASD. Summary of microbial composition, functional implications and therapeutic insights in ASD cases

Finding	Description	Key Citations
Microbiota Dysbiosis	Altered gut microbial composition in ASD individuals, including higher levels of *Clostridium*, *Desulfovibrio*; lower levels of *Bifidobacterium*, *Prevotella*, *Lactobacillus*; mixed changes in *Bacteroides* species.	[108, 110, 121]
Reduced Microbial Diversity	Children with ASD show lower gut microbial diversity and richness compared to NCs.	[103, 108, 112, 140]
Microbiota-Gut-Brain Axis	Bidirectional communication between the gut and brain mediated via the vagus nerve, immune signalling, and metabolites.	[121, 141, 142]
Leaky Gut/Increased Intestinal Permeability	ASD individuals may have impaired gut barrier function, allowing microbial by-products and toxins to enter circulation.	[143–146]
Neuroimmune Modulation	Neuroinflammation and immune activation are affected by gut microbiota imbalances, indicating brain function dysregulation in ASD.	[147–151]
Functional Metabolomic Changes	Systematic shifts in metabolic pathways associated with ASD, including amino-acid, carbohydrate and lipid imbalances likely contributing to neurodevelopmental differences and immune activation in ASD.	[121, 152–154]
Probiotics and Behavioural Effects	Probiotic treatment (i.e *Lactobacillus plantarum*, *Bifidobacterium longum*) improves behaviour in ASD and reduces GI symptoms.	[148, 155–157]
Faecal Microbiota Transplantation (FMT)	FMT consistently improves GI symptoms and behavior in ASD children, with sustained effects.	[116, 158–160]

the production of neuroactive compounds, modulation of the immune system, and alteration of gut-brain communication pathways [100]. It has become apparent that differences in microbial composition and diversity exist between individuals with ASD and neurotypical controls [101–113].

Notably, gastrointestinal comorbidities are more prevalent in children diagnosed with ASD compared to their neurotypical peers, with some studies suggesting a fourfold increase in the likelihood of experiencing GI symptoms [114]. Gastrointestinal issues commonly observed in individuals with ASD include abdominal pain, diarrhoea, and constipation [115]. A growing body of evidence clearly shows that children with ASD tend to exhibit lower microbial diversity, as well as alterations in the relative abundance of specific bacterial taxa [116]. Multiple studies have consistently shown a reduced abundance of beneficial bacteria, such as *Bifidobacteria* and *Lactobacillus*, coupled with an overgrowth of potentially pathogenic bacteria, like *Clostridia* and *Bacteroides* in individuals with ASD [117].

Although there is an abundance of data linking the diversity of bacterial communities colonising the gut of ASD patients, no direct link to a possible role of these microbes in the development of autism symptoms has been found [118–120].

A recent ground-breaking study employing a comprehensive multi-omics approach has provided evidence linking specific bacterial strains to the development of autism spectrum disorder (ASD). By integrating samples taken from urine, blood, and fecal matter from age-matched ASD patients and neurotypical (ND) controls, the study utilized RNA sequencing, metabolomics, and microbiomics to capture a holistic view of the host and microbial molecular landscapes. This integrative methodology enables the simultaneous examination of alterations in host gene expression, metabolic shifts, and bacterial community structures, which is critical given the multifactorial etiology of ASD [121]. From this multi-directional analysis, four groups of microbes stand out in ASD patients that differ from age-matched NT controls. These include the gut microbe *Bacteroides fragilis* which has been shown to improve symptoms in mice. This bacterium is also considered a next-generation probiotic agent for improving gastrointestinal symptoms [122]. Next, one bacterial signature that stands out in ASD patients, is the *Bifidobacterium* strain which is associated with early development and childhood [123, 124]. Whether the role of this bacterial strain is protective or delays gut maturation is not well understood. It has been suggested that the *Bifidobacterium longum* strain could alleviate autistic-like behaviours (repetitive behaviours, learning and memory ability and despair mood) [125, 126]. The sulphate-reducing bacteria (SRB) of the genus *Desulfovibrio* have also been found to be more abundant in children with ASD compared to healthy children [105, 111, 127]. Another genus of bacteria gaining attention in autism due to its immense dietary complexity is *Prevotella*. This bacterium has the capacity to metabolize complex carbohydrates and is found in increased numbers in carbohydrate-depleted diets [108, 128, 129] Children diagnosed with ASD often exhibit reduced levels of *Prevotella*, particularly *Prevotella copri* in their gut microbiota. Notably, in a comparative study utilising 16S rRNA gene sequencing to compare intestinal microflora between ASD patients and NT controls, it was discovered that the abundance of *P. copri* and other fermentative bacteria was lower in ASD-diagnosed children than in their neurotypical counterparts [108]. Comparing results across studies

highlights that the role of *P. copri* is complex and context-dependent. For example, while some investigations indicate an overall depletion of *Prevotella* in ASD [130], subsequent analyses reveal that sub-species level variation —exemplified by an increase in *P. copri* — is critical in modulating host metabolic pathways [131]. Multi-omic analysis reinforces this complexity by correlating *P. copri*-associated metabolic signatures to brain-associated gene expression profiles and pro-inflammatory cytokine patterns [121, 132]. This integrative approach underscores that microbe alterations in ASD are both microbial community- and strain-specific, indicating that *P. copri* may serve as a potential biomarker for a subset of ASD characterised by distinct metabolic disruptions.

Overall, these findings underscore the importance of strain-level analysis in the microbial ecology of ASD and pave the way for targeted interventions that might modulate the gut microbiome to improve clinical outcomes. Despite these advances, the inconsistent nature of results across various studies, which can be attributed to variations in study designs, small sample sizes, and the heterogeneity of the ASD microbiome, necessitates further research to validate these findings and elucidate the precise mechanisms by which gut microbiota influences the pathogenesis of ASD [133]. Future studies should aim for larger, more standardized cohorts, consider factors such as dietary habits and medication use, and employ advanced techniques such as metagenomics and metabolomics to gain a deeper understanding of the complex interplay between the gut microbiota and ASD [133–135].

MAPPING THE GUT MICROBIOME TO MULTI-OMICS

Current research conducted to understand the association between the gut microbiota and ASD has rapidly expanded with the use of technologies analysing the gut microbiome of ASD patients with regards to their neurotypical counterparts at different omics levels. Researchers have employed a variety of high-throughput and integrative approaches to elucidate the underlying molecular interactions between the host and its microbial residents. Multi-omics strategies now incorporate metagenomics, meta-transcriptomics, metabolomics, and the emerging field of small non-coding RNA (ncRNA) profiling, each contributing a unique perspective on the complex etiology of ASD. The results of these multi–omics studies have revealed many, although inconsistent, differences in microbial diversity in children with ASD compared to their neurotypical controls [120, 121]. Similarly, functional metagenomics and metabolic analyses have also shown strong, albeit inconclusive, differences between the two groups [119]. It is worth noting that differences in sequencing methods, data analysis pipelines and patient selection could contribute to the conflicting differences reported across studies [136].

Comparative analyses at other omic levels have further shown inconsistencies across studies [118], making it difficult to distinguish whether the results obtained are due to intrinsic biological differences among samples or are a result of experimental biases and insufficient statistical power that prevent meaningful results [121, 137]. In one of the latest multi-omic level analysis of the gut microbiota profiles in ASD, the discrepancies in experimental design, sample processing and result interpretation were taken into account and already published datasets were re-analysed and re-evaluated in an attempt to produce an integrated approach to the multitude of previous published datasets to date [121]. In detail, samples from ten cross-sectional microbiome datasets with fifteen additional omic datasets—including dietary records, metabolomics, cytokine profiles, and brain expression profiles—were combined in order to identify autism-specific patterns along the gut-brain axis. The integration of multiple omics platforms resulted in a more clear understanding of the functional architecture of autism, therefore establishing a more distinctive relationship between microbial communities and host physiological processes.

In another approach, advanced topic modelling was applied through latent Dirichlet allocation to multi-omic datasets (16S rRNA gene amplicon, shotgun metagenomic, metatranscriptomic, and untargeted metabolomic profiling) from ASD and NTD fecal samples. This approach pinpointed microbial processes and topics that differ between autistic and neurotypical children and identified specific metabolites — such as neurotransmitter precursors — that could serve as functional biomarkers of the disorder [138].

In addition to these high-throughput microbial and transcriptional assessments, metabolomic approaches have also been used to understand how microbial fermentation products affect neurological development. Microbial fermentation of dietary fibers produces short-chain fatty acids (SCFAs), which in turn may exert either beneficial or detrimental effects on both gut and neurological development in individuals with ASD [139]. Due to the multifaceted nature of autism, in order to understand the mechanisms by which alterations in gut microbial communities contribute to ASD via immune and neuroendocrine signalling pathways, multiple-omic levels are critical in understanding this complex interaction.

Therapeutic approaches targeting the gut microbiome in autism

Therapeutic approaches targeting the gut microbiome have emerged as a promising, though still evolving, area of research for autism. This field integrates multiple lines of evidence on the critical role the microbiota–gut–brain axis has in the heterogenic nature of the condition. In preclinical models, modifications of the gut microbiota have led to improvements in both gastrointestinal function and neurobehavioral outcomes, suggesting that the manipulation of gut microbes may directly impact brain function and behaviour [161, 162]. Therapeutic interventions aimed at restoring an eubiotic gut environment include a spectrum of approaches such as probiotics, prebiotics, antibiotics, and

fecal microbiota transplantation (FMT) [161, 163]. These microbial-based interventions have shown promise in a limited number of human trials [158, 164, 165].

Probiotics, in particular, have been extensively examined in both clinical and preclinical studies as a means to ameliorate GI symptoms and potentially modify core behavioral impairments associated with ASD [117, 166]. For example, several clinical studies with single or mixed probiotic strains have yielded promising results in mitigating gastrointestinal inflammation and restoring microbial equilibrium, although the outcomes remain heterogeneous and require larger-scale trials for definitive conclusions [117, 162]. Furthermore, probiotics have been shown to exert bidirectional effects on gut-brain communication, with some studies reporting improvements in core ASD symptoms, possibly by reducing gut permeability and modulating neuroinflammatory markers [117, 167]. Despite these advances, the field continues to confront challenges related to standardising treatment protocols, determining optimal strains or combinations, and establishing long-term efficacy, as well as understanding the interplay between genetic predisposition and environmental influences in ASD [161, 163].

Fecal microbiota transplantation (FMT) has emerged as a promising therapeutic intervention for addressing autism spectrum disorder (ASD) symptoms, particularly those associated with gastrointestinal (GI) dysfunction. Many children with ASD experience significant GI disturbances that correlate with increased behavioural symptom severity, suggesting a link between gut dysbiosis and neurological manifestations [168, 169]. Systematic reviews and clinical trials have demonstrated that FMT can lead to improvements in both behavioural outcomes and GI symptoms in paediatric populations with ASD [166, 169]. Conversely, FMT offers an alternative strategy that targets the complex microbiota environment of the gut by reintroducing a full complement of microbial communities, thereby directly influencing the MGB axis and potentially attenuating aberrant immune responses and metabolic disturbances linked to ASD [161, 170].

Recent investigations showed that FMT, by introducing a wider range of commensal microbes from a healthy donor, may correct the imbalance in the gut microbial community observed in ASD [171]. For instance, *Kang* et al. reported long-term benefits following a microbiota transfer therapy protocol that combined antibiotics, bowel cleansing, and subsequent FMT, observing improvements in both core behavioural symptoms and gastrointestinal disturbances [116, 172]. These findings suggest that re-establishing a balanced gut microbiota could modulate the microbiota–gut–brain axis, subsequently influencing neurodevelopment and behaviour [168, 171].

Additional studies support the therapeutic potential of FMT through various routes of administration tailored to the pediatric population. Research has demonstrated that both capsule-based and tube-delivered FMT approaches are feasible and can produce significant clinical responses in children with ASD [159]. Moreover, case reports and retrospective studies have reported enhanced gastrointestinal function as well as a reduction in behavioural dysfunction following FMT [173]. Evidence suggests that repeated courses of FMT may provide additive benefits, indicating that sustained modulation of the gut microbiota may be advantageous for symptom management in ASD [174].

Beyond clinical observations, preclinical models have provided mechanistic insights into the role of the gut microbiome in ASD. Animal studies illustrate that transplantation of faecal microbiota from ASD patients into germ-free or antibiotic-treated animals can induce autism-like behaviours, thus reinforcing the concept that microbiota alterations may play a causative role in the disorder [175]. Such studies underscore the relevance of the gut–brain axis, where microbial metabolites and signalling molecules can influence neural function and behaviour [176].

Despite encouraging early results, the field requires further randomized controlled trials and longer-term follow-up studies to definitively establish both efficacy and safety profiles, as well as to elucidate the precise mechanisms by which FMT mediates its effects on the central nervous system [166, 169, 177].

In summary, FMT represents a novel and potentially effective therapeutic strategy in ASD by targeting the gut dysbiosis that frequently accompanies both gastrointestinal and behavioural abnormalities in affected children [116, 168, 171]. While emerging data are encouraging, a comprehensive understanding of optimal protocols, long-term outcomes, and mechanistic pathways is required to firmly establish FMT in the therapeutic arsenal against ASD.

In summary, the current evidence supports the notion that microbial-based interventions aimed at restoring a healthy gut microbiome have the potential to be utilized as complementary therapies for ASD. The integration of approaches such as probiotics, prebiotics, and FMT into clinical practice could pave the way for personalized medicine strategies aimed at both alleviating gastrointestinal disturbances and moderating behavioral symptoms in autism. However, further rigorous, large-scale, and longitudinal clinical trials are indispensable to validate the efficacy and safety profiles of these interventions, and to unravel the precise mechanisms by which the gut microbiota influence neurodevelopment and behaviour.

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MAK: drafting the article or revising it critically for important intellectual content, writing.

SV: validation, formal analysis.

PS: analysis and interpretation of data.

SM: analysis and interpretation of data.

VP: final approval of the version to be submitted.

MC: conceptualization methodology and design of the study, data curation, writing—original draft preparation, writing—review and editing.

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