World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

ASD and the gut microbiota: Emerging insights into autism treatment

Yeshaswini Katkoori [1,*], Nikhil Ravula [2] and Sai Prajwal Reddy Narahari [3]

[1] *Department of Medicine, Osmania Medical College, Hyderabad, Telangana, India.*
[2] *Department of Internal Medicine, St Vincent Hospital, Worcester, Massachusetts, USA.*
[3] *Department of Medicine, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 19(03), 396–402

Publication history: Received on 05 August 2024; revised on 14 September 2024; accepted on 16 September 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.3.0623

Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, social interaction, and restrictive, repetitive behaviors. Changes in diagnostic criteria and better awareness have led to a higher prevalence of autism. ASD has a heterogenous etiology with genetics and environmental factors playing major roles. GI symptoms like constipation, diarrhea and abdominal discomfort are prevalent in children with ASD and affect up to 70% of patients. Recent research has drawn attention to gut dysbiosis which has been linked to gastrointestinal and neurodevelopmental symptoms. Increased intestinal permeability and microbial metabolite differences have also been implicated in the pathophysiology of ASD, with certain microbial species, like Clostridia playing a major role. Probiotics, ketogenic diets and fecal microbiota transplantation are all therapeutic interventions that have shown potential in reducing ASD symptoms. However, more research is needed to establish the safety and long-term efficacy of these interventions. This paper explores the relationship between gut microbiota and ASD and its potential as a therapeutic target. Further studies such as using a multi-omics approach would be beneficial to better understand the interactions of gut microbes and ASD, possibly allowing for novel therapeutic interventions.

Keywords: ASD; gut microbiota; Autism treatment; Neurodevelopmental disorder

1. Introduction to ASD

Autism spectrum disorder is a neurodevelopmental disorder encompassing 2 domains of deficits in social communication and social interaction & restricted, repetitive patterns of behavior, interest and activities[1]. There has been a significant increase in the prevalence of ASD in the past few decades, precisely from 1.1% in 2008 to 2.3% in 2018. This is likely associated with changes in the criteria for diagnosis, more awareness, and better performing screening and diagnostic modalities. Since autism also lacks specific biomarkers, making a diagnosis is difficult [2,3]. Autism is mainly associated with motor abnormalities (in about 79%), gastrointestinal symptoms (in up to 70%) and sleep disorders (in about 50-80%). Intellectual disability (at about 45%) and epilepsy (up to 30%) are also seen with autism spectrum disorder. [4]

ASD is very heterogenous in its etiology which is influenced by age and developmental factors. Genetics play a crucial role in the etiology of ASD. This can be seen in studies done in twins that showed heritability ranging from 64-91% with little influence of environmental factors.[4] Only one-third of the instances of ASD can be attributed to genetic causes. It's likely that the pathophysiology of ASD is influenced by environmental variables and epigenetic effects.[10] Autism affects males more than females on a 4:1 ratio. [5] An important risk factor for an increased likelihood of ASD is advanced maternal and paternal age. Inadequate maternal education and socioeconomic position also increase the vulnerability to ASD. [6] Some prenatal factors like valproate intake, maternal diabetes, selective serotonin reuptake inhibitor treatment, toxic chemical exposure, maternal infection, physical health and overall condition of the mother

* Corresponding author: Yeshaswini Katkoori

were shown to influence the onset of ASD. Fetal complications during birth, cesarean delivery, hypoxia, umbilical cord complications can also be risk factors for ASD. Postnatally, antibiotic intake, nutritional factors and breastfeeding can influence the onset of ASD. [7,8,9]

2. Gastrointestinal involvement in ASD

Gastrointestinal symptoms are frequently reported in children with ASD, with a variety of presentations such as constipation, diarrhea, food allergies, abdominal pain, reflux, vomiting, gaseousness and foul smelling stools.[10] Out of these, constipation seems to be the most prevalent reported symptom[11,12], although some studies have shown that chronic diarrhea, gaseousness, abdominal discomfort and distension were the most frequent GI symptoms. [13] GI symptoms are four times more prevalent in people with ASD than the general population. [11] This is substantiated by another study where children with asd experienced more GI symptoms than comparison groups with a standardized mean difference of 0.82 (0.24), and an odds' ratio of 4.42 (95% CI, 1.90-10.28). The analysis also reflected higher rates of symptoms like diarrhea, constipation and abdominal pain. [14]

Even though constipation and food restriction were the most common GI symptoms in both ASD and normal development children, they were found to be more severe in ASD patients. Those children with GI symptoms and ASD were found to have more anxiety, somatic issues and complaints than children with ASD and no GI symptoms. [15] Similarly, one study found a strong association between constipation and language impairment in children with ASD, implying the need to address and treat the GID. [12] It also supported the concerns of parents of children with ASD who were attentive and aware of some form of GI distress, even if they didn't know its exact nature. [12]

3. Gut Microbiome

There are trillions of microorganisms coexisting in the human body that are essential to many physiologic functions like digestion, metabolism, and immunologic response. Of these, the gut microbiome in particular is essential for producing vitamins as well. A well balanced and varied gut microbiome is crucial for better health outcomes. There are many individual differences in the body's microbial population that are affected by food, lifestyle, genetics and environmental factors. When these gut microbiota are altered, disrupting the equilibrium, it is referred to as dysbiosis. This dysbiosis has been linked to many psychiatric disorders such as mood disorders, schizophrenia and anxiety disorders. [16] There are many changes in GI physiology in ASD patients including microbiota alterations, increased intestinal permeability, gut infection. Dysbiosis at a young age shows its effects on health throughout life, therefore it is important to address changes in childhood. A strong indicator of this is that many autistic children take high doses of oral antibiotics in the early years of life. [17]

In 2019, Sharon and colleagues studied the behavior of germ-free mice after being colonized with fecal microbiota from children with ASD. They noticed more autistic behavior in mice colonized with ASD microbiota from ASD showed an alternative splicing of ASD-related genes in the brain. [18,19]

Clostridium bacterial concentrations were found to be higher in ASD patients. [18,20] The neurotoxins that Clostridium makes were shown to exacerbate autistic symptoms according to the Childhood Autism Rating scale. This scale is normally used to determine the severity of ASD.[21,22] More evidence of the influence of Clostridium in ASD can be shown by the improvement in symptoms by the oral vancomycin treatment. [20]

Certain bacterial concentrations were found to be decreased such as Bifidobacterium, Enterococcus, and Bacteroidetes.[18,20,23] The Bacteroidetes phylum is responsible for polysaccharide digestion and hence this research supports the causality of the theory that ASD patients have difficulty in the digestion of carbohydrates. [20,24] The microbial alterations in ASD patients are not always consistent changed as seen between many studies. [20,24] This could be due to changes in aspects like gender, age, diet, population and severity of autism.

4. Intestinal permeability and metabolite differences in ASD

Increased intestinal permeability and microbial metabolites is a major mechanism in disruption of gastrointestinal functioning. Autistic children and their siblings were found to have increased gut permeability in comparison to their controls. [22] This increased gut permeability was predicted to be a result of decreased expression of barrier forming proteins and increased expression of pore forming proteins of tight junctions. [25]

The production of LPS and proinflammatory cytokines by Gram negative bacteria have been implied as factors for disruption of the gut brain axis and blood brain barrier in patients with ASD. [25,26]

This "leaky gut" in ASD patients helps toxins cross the gut barrier to the organs and form an autoimmune response. This could be the reason behind the peculiar eating habits of autistic patients. Some of the proteins involved in this food sensitivity are lysozyme, calprotectin, and zonulin. [27] I-FABP is a biomarker of intestinal epithelial damage. An increase in I-FABP was found to be correlated with more severe deficits in communication, social interaction, maladaptive behavior and overall more severe behavioral phenotypes in very young children with ASD. [28] Similarly, haptoglobin, an acute phase reactant, was also found to be correlated to behaviour. [28]

SCFA's are known to influence early brain development by affecting dopamine and serotonin secretion on crossing the blood brain barrier. [27] These SCFA's are important in the regulation of immune cell response by modulating the secretion of T cell cytokines. [29?] This is of significance as SCFA's are increased in stool and serum of children with ASD. SCFA producing gut bacteria such as Clostridia, Desulfovibrio and Bacteroides are also increased in feces of children with ASD. [30,31]

Gut microbial composition is affected by Enterochromaffin cells producing 5-HT. [32] 5-HT and severity of GI symptoms were found to be positively correlated. [33] A Clostridium species overgrowth biomarker- a phenylalanine metabolite [3-(3-hydroxyphenyl)-3-hydroxypropanoic acid] was found to be elevated in the urine of patients with ASD. It was also found to be associated with ASD-like behaviors in mice models. [34?]

Despite all these studies that state otherwise, other studies showed no changes in gut permeability in autistic children. This implies that a disturbance of the gut barrier is not always a symptom of autism but mainly was found in ASD children that had intestinal abnormalities. [35,36] Further research and studies are needed in this area to understand the importance of the intestinal barrier in the pathogenesis of gastrointestinal dysfunction in ASD.

5. Therapeutic implications of Gut Microbiome in ASD

Probiotics are living microorganisms given as supplementation treatment to have positive health outcomes. They help by strengthening the intestinal barrier, stimulating an immune response, reducing the overgrowth of pathogens, increased mucine expression and producing antioxidants and vitamins. [37] In a case study, where ASD patients with serious cognitive impairment were treated for 4 weeks with VSL#3, a mixture of live cells of 10 different probiotics, autistic symptoms and severity of GI symptoms. [38] They also conducted 4 month supplementation with 3 probiotics containing *Lactobacillus* strains, 2 *Bifidobacterium* strains, a *Streptococcus* strain which caused the ratio of *Bacteroidetes/Firmicutes* to stabilize. It also caused a decrease in *Bifidobacterium* and *Desulfovibrio* species. [38] Similarly improved GI symptoms and autistic behaviours were seen with 3 month supplementation with probiotics having 3 strains of *Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacterium longus*. This supplementation also caused an increase in the beneficial bacteria Bifidobacteria and Lactobacilli. [39] Multiple studies have shown that strains of Lactobacillus decrease social impairments in animal models. [19] Supplementation with Lactobacillus acidophilus strain showed lower amounts of D-arabinitol in the urine of ASD children and an enhanced ability to follow instructions. [40] This decrease in autistic symptoms on treatment with probiotics shows the influence of gut microbiota on behavioral symptoms and possibly the etiology of ASD. [41] Such treatment of autistic symptoms with probiotics can improve compliance and adherence of these patients to other rehabilitation and educational treatments. It would also help reduce the overall costs of the disease. [37]

Ketogenic diets have shown to have an effect on the symptoms of ASD patients. Research in human and animal models has shown potential positive effects of ketogenic diets with high-fat content (65-90%) used to lower ASD symptoms. [42] They have shown to possibly trigger reductions in total gut microbial counts and compositional remodeling in the animal model, highlighting their ability to mitigate some of the neurological symptoms associated with ASD. [43] Contrary to this, in terms of the maternal aspect of the rodent model, mothers fed with a high-fat diet eight weeks before mating had offspring showing impaired social interaction and repetitive behaviors similar to ASD. [44] High- fat diets may regulate the gut microbiome by accelerated growth of bile-tolerant bacteria and by reducing microbial diversity, especially by saturated fatty acids. This may increase the risk of gastrointestinal disease. Omega-3 has anti-inflammatory properties and exerts an overall positive effect on the gut microbiome. [45] This shows us that varying fatty acid compositions along with a structured ketogenic diet could have many therapeutic implications on gastrointestinal symptoms of ASD. Another interesting finding regarding therapeutic diets for ASD was that of a gluten-free and casein-free diet significantly reducing intestinal permeability.[46]

Nutritional deficiencies of vitamins, minerals, and fatty acids have commonly been observed in children with ASD. Vitamin E, vitamin D, vitamin B12, pantothenic acid, folate, and biotin were found in lower concentrations in ASD patients. Concentrations of calcium, magnesium, iodine, iron, chromium, and selenium were also found to be lower in children in ASD. [47],[48] Further research into the extent and types of these nutritional deficiencies needs to be explored in order for supplements to be a therapeutic option. Omega-3 fatty acids are one such food supplement considered to be a complementary and therapeutic agent. [49]

Fecal microbiota transplant is beneficial to patients with ASD. Microbiota Transfer Therapy encompassing extended fecal microbiota transplant, antibiotic treatment, a bowel cleanse, and a stomach-acid suppressant was found to cause significant improvements in gastrointestinal symptoms and those of ASD. It even led to an improvement in social skill deficits. [50] Many of the changes from fecal microbiota transplants were found to be lasting and even improved two years after completion of the treatment. [51] Post treatment with microbiota transplants, plasma and fecal metabolite profiles of ASD patients became more similar to their typical developing peers. [52]

6. Future direction

The increasing rates of Autism Spectrum Disorder (ASD) have the need to identify accurate etiological and pathogenetic factors. Among these factors, evidence on the impact of gut dysbiosis in the etiology of ASD has accumulated over the last few decades. Gut dysbiosis plays a crucial role in the health of the gastrointestinal (GI) tract as well as in central nervous system (CNS) development and neurophysiological homeostasis. Numerous pathways through which gut microbes exert their effects have been explored, and further research into these pathways could pave the way for novel therapeutic avenues and an improvement in the quality of life for ASD patients.

However, interventions targeting gut dysbiosis require further evaluation, particularly through standardized treatment regimens in larger randomized controlled trials. Fecal Microbiota Transplantation (FMT) and Microbiota Transfer Therapy (MTT) appear to be promising treatments that help restore gut dysbiosis in ASD patients. Nonetheless, a long-term outlook cannot yet be guaranteed, and the tolerance and safety of FMT still need further study. Utilizing larger sample sizes in these studies may aid in identifying specific groups of microbes that could play a definitive role in managing or potentially curing ASD.

The extensive role of microbes in ASD is evident from an etiological perspective and their association with ASD symptoms. Although gut dysbiosis has been linked to ASD pathogenesis, it is unlikely that a single microbe will be identified as a hallmark of ASD. This is partly due to inconsistent analytical techniques, such as the use of different scales for evaluating ASD symptoms, and the lack of highly accurate criteria and biomarkers for diagnosis. Additionally, the presence of various variables among study participants, such as age, sex, dietary lifestyles, and GI symptoms, complicates analysis. Existing studies have primarily focused on changes in gut bacteria, with few or no studies investigating other gut microbiota like fungi, protozoa, viruses, and archaea. Implementing a multi-omics approach in future research could provide more comprehensive insights

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] American Psychiatric Association. (2022). Neurodevelopmental disorders. In *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.)

[2] Hirota T, King BH. Autism Spectrum Disorder: A Review. JAMA. 2023 Jan 10;329(2):157-168. doi: 10.1001/jama.2022.23661. PMID: 36625807.

[3] Fombonne E. Editorial: The rising prevalence of autism. J Child Psychol Psychiatry. 2018 Jul;59(7):717-720. doi: 10.1111/jcpp.12941. PMID: 29924395.

[4] Rylaarsdam L, Guemez-Gamboa A. Genetic Causes and Modifiers of Autism Spectrum Disorder. Front Cell Neurosci. 2019 Aug 20;13:385. doi: 10.3389/fncel.2019.00385. PMID: 31481879; PMCID: PMC6710438.

[5] Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry. 2016 May;57(5):585-95. doi: 10.1111/jcpp.12499. Epub 2015 Dec 27. PMID: 26709141; PMCID: PMC4996332.

[6] Lung FW, Chiang TL, Lin SJ, Lee MC, Shu BC. Advanced Maternal Age and Maternal Education Disparity in Children with Autism Spectrum Disorder. Matern Child Health J. 2018 Jul;22(7):941-949. doi: 10.1007/s10995-018-2470-9. PMID: 29411255.

[7] Bölte S, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. Cell Mol Life Sci. 2019 Apr;76(7):1275-1297. doi: 10.1007/s00018-018-2988-4. Epub 2018 Dec 20. PMID: 30570672; PMCID: PMC6420889.

[8] Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. Medicine (Baltimore). 2017 May;96(18):e6696. doi: 10.1097/MD.0000000000006696. PMID: 28471964; PMCID: PMC5419910.

[9] Yu L, Wu Y, Wu BL. Genetic architecture, epigenetic influence and environment exposure in the pathogenesis of Autism. Sci China Life Sci. 2015 Oct;58(10):958-67. doi: 10.1007/s11427-015-4941-1. PMID: 26490976.

[10] Srikantha P, Mohajeri MH. The Possible Role of the Microbiota-Gut-Brain-Axis in Autism Spectrum Disorder. Int J Mol Sci. 2019 Apr 29;20(9):2115. doi: 10.3390/ijms20092115. PMID: 31035684; PMCID: PMC6539237.

[11] Marler S, Ferguson BJ, Lee EB, Peters B, Williams KC, McDonnell E, Macklin EA, Levitt P, Margolis KG, Beversdorf DQ, Veenstra-VanderWeele J. Association of Rigid-Compulsive Behavior with Functional Constipation in Autism Spectrum Disorder. J Autism Dev Disord. 2017 Jun;47(6):1673-1681. doi: 10.1007/s10803-017-3084-6. PMID: 28289979; PMCID: PMC5526215.

[12] Gorrindo P, Williams KC, Lee EB, Walker LS, McGrew SG, Levitt P. Gastrointestinal dysfunction in autism: parental report, clinical evaluation, and associated factors. Autism Res. 2012 Apr;5(2):101-8. doi: 10.1002/aur.237. PMID: 22511450; PMCID: PMC3335766.

[13] Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. J Pediatr. 1999 Nov;135(5):559-63. doi: 10.1016/s0022-3476(99)70052-1. PMID: 10547242.

[14] McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. Pediatrics. 2014 May;133(5):872-83. doi: 10.1542/peds.2013-3995. PMID: 24777214.

[15] Fulceri F, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, Calderoni S, Muratori F. Gastrointestinal symptoms and behavioral problems in preschoolers with Autism Spectrum Disorder. Dig Liver Dis. 2016 Mar;48(3):248-54. doi: 10.1016/j.dld.2015.11.026. Epub 2015 Dec 11. PMID: 26748423.

[16] Fond G, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N, Dickerson F, Macgregor A, Boyer L, Dargel A, Oliveira J, Tamouza R, Leboyer M. The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review. Pathol Biol (Paris). 2015 Feb;63(1):35-42. doi: 10.1016/j.patbio.2014.10.003. Epub 2014 Nov 2. PMID: 25468489.

[17] Kang DW, Park JG, Ilhan ZE, Wallstrom G, Labaer J, Adams JB, Krajmalnik-Brown R. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. PLoS One. 2013 Jul 3;8(7):e68322. doi: 10.1371/journal.pone.0068322. PMID: 23844187; PMCID: PMC3700858.

[18] Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mazmanian SK. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell. 2019 May 30;177(6):1600-1618.e17. doi: 10.1016/j.cell.2019.05.004. PMID: 31150625; PMCID: PMC6993574.

[19] Needham BD, Tang W, Wu WL. Searching for the gut microbial contributing factors to social behavior in rodent models of autism spectrum disorder. Dev Neurobiol. 2018 May;78(5):474-499. doi: 10.1002/dneu.22581. Epub 2018 Feb 20. PMID: 29411548.

[20] Settanni CR, Bibbò S, Ianiro G, Rinninella E, Cintoni M, Mele MC, Cammarota G, Gasbarrini A. Gastrointestinal involvement of autism spectrum disorder: focus on gut microbiota. Expert Rev Gastroenterol Hepatol. 2021 Jun;15(6):599-622. doi: 10.1080/17474124.2021.1869938. Epub 2021 Jan 5. PMID: 33356668.

[21] Sivamaruthi BS, Suganthy N, Kesika P, Chaiyasut C. The Role of Microbiome, Dietary Supplements, and Probiotics in Autism Spectrum Disorder. Int J Environ Res Public Health. 2020 Apr 12;17(8):2647. doi: 10.3390/ijerph17082647. PMID: 32290635; PMCID: PMC7215504.

[22] van De Sande MM, van Buul VJ, Brouns FJ. Autism and nutrition: the role of the gut-brain axis. Nutr Res Rev. 2014 Dec;27(2):199-214. doi: 10.1017/S0954422414000110. Epub 2014 Jul 8. PMID: 25004237.

[23] Strati F, Cavalieri D, Albanese D, De Felice C, Donati C, Hayek J, Jousson O, Leoncini S, Renzi D, Calabrò A, De Filippo C. New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome. 2017 Feb 22;5(1):24. doi: 10.1186/s40168-017-0242-1. PMID: 28222761; PMCID: PMC5320696.

[24] Pulikkan J, Mazumder A, Grace T. Role of the Gut Microbiome in Autism Spectrum Disorders. Adv Exp Med Biol. 2019;1118:253-269. doi: 10.1007/978-3-030-05542-4_13. PMID: 30747427.

[25] Fiorentino M, Sapone A, Senger S, Camhi SS, Kadzielski SM, Buie TM, Kelly DL, Cascella N, Fasano A. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Mol Autism. 2016 Nov 29;7:49. doi: 10.1186/s13229-016-0110-z. PMID: 27957319; PMCID: PMC5129651.

[26] Coretti L, Paparo L, Riccio MP, Amato F, Cuomo M, Natale A, Borrelli L, Corrado G, Comegna M, Buommino E, Castaldo G, Bravaccio C, Chiariotti L, Berni Canani R, Lembo F. Gut Microbiota Features in Young Children With Autism Spectrum Disorders. Front Microbiol. 2018 Dec 19;9:3146. doi: 10.3389/fmicb.2018.03146. Erratum in: Front Microbiol. 2019 May 03;10:920. doi: 10.3389/fmicb.2019.00920. PMID: 30619212; PMCID: PMC6305749.

[27] Al-Ayadhi L, Zayed N, Bhat RS, Moubayed NMS, Al-Muammar MN, El-Ansary A. The use of biomarkers associated with leaky gut as a diagnostic tool for early intervention in autism spectrum disorder: a systematic review. Gut Pathog. 2021 Sep 13;13(1):54. doi: 10.1186/s13099-021-00448-y. PMID: 34517895; PMCID: PMC8439029.

[28] Teskey G, Anagnostou E, Mankad D, Smile S, Roberts W, Brian J, Bowdish DME, Foster JA. Intestinal permeability correlates with behavioural severity in very young children with ASD: A preliminary study. J Neuroimmunol. 2021 Aug 15;357:577607. doi: 10.1016/j.jneuroim.2021.577607. Epub 2021 May 12. PMID: 34044209.

[29] Lagod PP, Naser SA. The Role of Short-Chain Fatty Acids and Altered Microbiota Composition in Autism Spectrum Disorder: A Comprehensive Literature Review. Int J Mol Sci. 2023 Dec 13;24(24):17432. doi: 10.3390/ijms242417432. PMID: 38139261; PMCID: PMC10743890.

[30] De Angelis M, Piccolo M, Vannini L, Siragusa S, De Giacomo A, Serrazzanetti DI, Cristofori F, Guerzoni ME, Gobbetti M, Francavilla R. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. PLoS One. 2013 Oct 9;8(10):e76993. doi: 10.1371/journal.pone.0076993. PMID: 24130822; PMCID: PMC3793965.

[31] Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 2011 Mar 16;11:22. doi: 10.1186/1471-230X-11-22. PMID: 21410934; PMCID: PMC3072352.

[32] Fattorusso A, Di Genova L, Dell'Isola GB, Mencaroni E, Esposito S. Autism Spectrum Disorders and the Gut Microbiota. Nutrients. 2019 Feb 28;11(3):521. doi: 10.3390/nu11030521. PMID: 30823414; PMCID: PMC6471505.

[33] Iglesias-Vázquez L, Van Ginkel Riba G, Arija V, Canals J. Composition of Gut Microbiota in Children with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Nutrients. 2020 Mar 17;12(3):792. doi: 10.3390/nu12030792. PMID: 32192218; PMCID: PMC7146354.

[34] Shaw W. Increased urinary excretion of a 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of Clostridia spp. in the gastrointestinal tract, in urine samples from patients with autism and schizophrenia. Nutr Neurosci. 2010 Jun;13(3):135-43. doi: 10.1179/147683010X12611460763968. PMID: 20423563.

[35] Dalton N, Chandler S, Turner C, Charman T, Pickles A, Loucas T, Simonoff E, Sullivan P, Baird G. Gut permeability in autism spectrum disorders. Autism Res. 2014 Jun;7(3):305-13. doi: 10.1002/aur.1350. Epub 2013 Dec 12. PMID: 24339339.

[36] Kushak RI, Buie TM, Murray KF, Newburg DS, Chen C, Nestoridi E, Winter HS. Evaluation of Intestinal Function in Children With Autism and Gastrointestinal Symptoms. J Pediatr Gastroenterol Nutr. 2016 May;62(5):687-91. doi: 10.1097/MPG.0000000000001174. PMID: 26913756.

[37] Santocchi E, Guiducci L, Fulceri F, Billeci L, Buzzigoli E, Apicella F, Calderoni S, Grossi E, Morales MA, Muratori F. Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on

clinical, biochemical and neurophysiological parameters. BMC Psychiatry. 2016 Jun 4;16:183. doi: 10.1186/s12888-016-0887-5. PMID: 27260271; PMCID: PMC4893248.

[38] Grossi E, Melli S, Dunca D, Terruzzi V. Unexpected improvement in core autism spectrum disorder symptoms after long-term treatment with probiotics. SAGE Open Med Case Rep. 2016 Aug 26;4:2050313X16666231. doi: 10.1177/2050313X16666231. PMID: 27621806; PMCID: PMC5006292.

[39] Shaaban SY, El Gendy YG, Mehanna NS, El-Senousy WM, El-Feki HSA, Saad K, El-Asheer OM. The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. Nutr Neurosci. 2018 Nov;21(9):676-681. doi: 10.1080/1028415X.2017.1347746. Epub 2017 Jul 7. PMID: 28686541.

[40] Kałużna-Czaplińska J, Błaszczyk S. The level of arabinitol in autistic children after probiotic therapy. Nutrition. 2012 Feb;28(2):124-6. doi: 10.1016/j.nut.2011.08.002. Epub 2011 Nov 12. PMID: 22079796.

[41] Critchfield JW, van Hemert S, Ash M, Mulder L, Ashwood P. The potential role of probiotics in the management of childhood autism spectrum disorders. Gastroenterol Res Pract. 2011;2011:161358. doi: 10.1155/2011/161358. Epub 2011 Oct 26. PMID: 22114588; PMCID: PMC3205659.

[42] Sivamaruthi BS, Suganthy N, Kesika P, Chaiyasut C. The Role of Microbiome, Dietary Supplements, and Probiotics in Autism Spectrum Disorder. Int J Environ Res Public Health. 2020 Apr 12;17(8):2647. doi: 10.3390/ijerph17082647. PMID: 32290635; PMCID: PMC7215504.

[43] Newell C, Bomhof MR, Reimer RA, Hittel DS, Rho JM, Shearer J. Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. Mol Autism. 2016 Sep 1;7(1):37. doi: 10.1186/s13229-016-0099-3. PMID: 27594980; PMCID: PMC5009541.

[44] Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. Cell. 2016 Jun 16;165(7):1762-1775. doi: 10.1016/j.cell.2016.06.001. PMID: 27315483; PMCID: PMC5102250.

[45] Kittana M, Ahmadani A, Al Marzooq F, Attlee A. Dietary Fat Effect on the Gut Microbiome, and Its Role in the Modulation of Gastrointestinal Disorders in Children with Autism Spectrum Disorder. Nutrients. 2021 Oct 27;13(11):3818. doi: 10.3390/nu13113818. PMID: 34836074; PMCID: PMC8618510.

[46] de Magistris L, Familiari V, Pascotto A, Sapone A, Frolli A, Iardino P, Carteni M, De Rosa M, Francavilla R, Riegler G, Militerni R, Bravaccio C. Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr. 2010 Oct;51(4):418-24. doi: 10.1097/MPG.0b013e3181dcc4a5. PMID: 20683204.

[47] Berding K, Donovan SM. Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs. Nutr Rev. 2016 Dec;74(12):723-736. doi: 10.1093/nutrit/nuw048. PMID: 27864534.

[48] Ranjan S, Nasser JA. Nutritional status of individuals with autism spectrum disorders: do we know enough? Adv Nutr. 2015 Jul 15;6(4):397-407. doi: 10.3945/an.114.007914. PMID: 26178024; PMCID: PMC4496734.

[49] Bent S, Bertoglio K, Hendren RL. Omega-3 fatty acids for autistic spectrum disorder: a systematic review. J Autism Dev Disord. 2009 Aug;39(8):1145-54. doi: 10.1007/s10803-009-0724-5. Epub 2009 Mar 31. PMID: 19333748; PMCID: PMC2710498.

[50] Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL, Roux S, Sadowsky MJ, Lipson KS, Sullivan MB, Caporaso JG, Krajmalnik-Brown R. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017 Jan 23;5(1):10. doi: 10.1186/s40168-016-0225-7. PMID: 28122648; PMCID: PMC5264285.

[51] Kang DW, Adams JB, Coleman DM, Pollard EL, Maldonado J, McDonough-Means S, Caporaso JG, Krajmalnik-Brown R. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Sci Rep. 2019 Apr 9;9(1):5821. doi: 10.1038/s41598-019-42183-0. PMID: 30967657; PMCID: PMC6456593.

[52] Qureshi F, Adams J, Hanagan K, Kang DW, Krajmalnik-Brown R, Hahn J. Multivariate Analysis of Fecal Metabolites from Children with Autism Spectrum Disorder and Gastrointestinal Symptoms before and after Microbiota Transfer Therapy. J Pers Med. 2020 Oct 2;10(4):152. doi: 10.3390/jpm10040152. PMID: 33023268; PMCID: PMC7712156