ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Research Article

GUT BRAIN AXIS IN AUTISM SPECTRUM DISORDERS - AYURVEDIC PERSPECTIVE

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ABSTRACT

Autism spectrum disorder (ASD) constitutes a group of brain developmental disorders, and it is defined by stereotyped behaviour and deficits in communication and social interaction. The prevalence of ASD has shown an alarming increase in the recent decades ending up to 1 in 90 children. The exact cause of ASD is still not known. Research studies have focused on genetic causes, dysregulation of the immune system, inflammation, exposure to environmental toxicants, and the defective gut microbiota. Accumulating evidence demonstrates that gastrointestinal symptoms, such as abdominal pain, gaseousness, diarrhea, constipation and flatulence, are a common comorbidity in patients with ASD. The gut consists of millions of microbiota, and we hypothesize that the microbiota and its metabolites might be involved in the pathophysiology of ASD. In Ayurveda all Psycho social abnormalities have been included under the category of *Unmada*. A defective digestive and metabolic function is postulated as the root cause of *Unmada*, leading to systemic accumulation of metabolic wastes (Dhatugataama). The metabolic wastes act as systemic toxins and impair the functional integrity of brain. An observational study was carried out in the outpatient section of the Department of Kaumarabhrithya, Govt. Ayurveda College Hospital for Women and Children, Poojappura, Thiruvananthapuram in 122 children with ASD. Data pertaining to Socio demographic aspects and clinical manifestations were recorded and its prevalence rate was calculated. It was noted that 54% of the cases showed an evident disturbance in the digestive mechanism. Constipation was complained by 28% of cases, bloated abdomen by 16%, irritable bowel by 8%, increased flatulence by 7% and recurrent diarrhoea by 3%. Although these studies did not show a cause-effect relationship between GI symptoms and ASD, the findings suggest that the gut plays an important role in the etiology of ASD. Ayurvedic treatment strategies that modulate the gut microbiota might constitute a potential therapy for patients with ASD.

KEYWORDS: Autism Spectrum Disorders, gut microbiome, gut brain axis, Ayurveda, *Ama*.

INTRODUCTION

ASD is one among the most enigmatic forms of disability mainly due to the socio behavioural attributes of the diseased. ASD includes Autism, Asperger syndrome, Childhood Disintegrative Disorder and Pervasive developmental disorders not otherwise specified. It involves severe difficulties in basic aspects of social behaviour such as eye contact, facial expression, unusual gestures, diminished responsiveness, pragmatic deficits, neologism, lack of emotions in speech, unusual response to sensory stimuli etc. This group of neuropsychiatric disorders show specific delay or deviance in social, communicative and cognitive development with developmental regression, absence of protodeclarative pointing, abnormal reaction to environmental stimuli, abnormal social interests, absence of symbolic play and so on. Global prevalence of ASD ranges from 0.07% to 1.8%.[1] A population study conducted in nine different centres over five zones in India was concluded with a prevalence rate of 1.2%.[2] Recent decades have witness an alarming increase in prevalence of this disorder all over the world. Although the exact cause of ASD is still not known, the main findings emphasize the role of genetic and environmental factors in the development of autistic behaviour.[3] Many studies have focused on genetic causes, dysregulation of the immune system, inflammation, exposure to environmental toxicants, and the gut microbiota.[4] Environmental factors are also likely to interact with the genetic profile and cause aberrant change in brain growth, neuronal development and functional connectivity.

Gut Microbiome

We coexist with vast populations of microbial species that make a host out of the human body. It has been estimated that up to 100 trillion microbial cells make a home out of us,[5] and likely outnumber

human body cells by an order of magnitude[6], leading some to term the human microbiome our "second genome."[7] Increasingly, it has become clear that these constellations of microbial species are a partner in homeostasis, and when the balance is tipped away from the healthy microbiome there can be a negative outcome on human health.[8] The gut consists of millions of microbiota, and we hypothesize that the microbiota and its metabolites might be involved in the pathophysiology of ASD. Several articles have reviewed the influence of the gut microbiota on the animal central nervous system (CNS) and suggested the existence of a microbiota gut-brain axis.[9] The microbiota-gut-brain axis is likely the method of communication between the brain and the gut microbiota. [10]

This article reviews the role of the gut microbiota in the pathology of ASD. Many studies have shown alterations in the composition of the fecal flora and metabolic products of the gut microbiome in patients with ASD. The gut microbiota influences brain development and behaviors through the neuroendocrine, neuroimmune and autonomic nervous systems. In addition, an abnormal gut microbiota is associated with several diseases, such as inflammatory bowel disease (IBD), ASD and mood disorders. [11]

Accumulating evidence demonstrates that gastrointestinal (GI) symptoms, such as abdominal pain, gaseousness, diarrhea, constipation and flatulence, are a common comorbidity in patients with ASD. The prevalence of GI symptoms ranges from 23 to 70% in children with ASD.[12] Furthermore, the observed GI symptoms are associated with the severity of ASD.[13,14] The gut microbiota is directly or indirectly associated with ASD symptoms, in part by influencing the immune system and metabolism. [15,16] A higher percentage of abnormal intestinal permeability was observed in 36.7% of patients with ASD and their relatives (21.2%) compared with control children (4.8%).[17] An increased intestinal permeability results in a higher antigenic load from the gastrointestinal tract. Lymphocytes and ASD-associated cytokines, such as interleukin-1β (IL-1β), IL-6, interferon-γ (IFN-γ), and tumor necrosis factor-a (TNF-α), are present in the circulation and cross the blood-brain barrier (BBB). Subsequently, IL-1β and TNF-α bind to brain endothelial cells and induce immune responses in the brain.[18,19] Immune responses to toxins produced by pathogenic microbiota and focal inflammation increase gut permeability.

An impaired intestinal barrier is observed in response to infection or stress, which allows the translocation of the gut bacteria across the intestinal wall and into the mesenteric lymphoid tissue. [20] IgE-mediated allergic immune response in the intestine increases the 5-hydroxytryptamine (5-HT) levels and decreases the 5-hydroxyindoleacetic acid (5-HIAA) levels in the intestine. It also reduces social communication and increases repetitive behavior. The pathway via which the microbiota communicate with the brain can also involve neurotransmitters. The gut microbiota produces neuroactive compounds such as dopamine (DA), 5-HT, γ-aminobutyric acid (GABA) and histamine, which activate or inhibit central neurons through the vagus nerve[21] Serotonin, which is synthesized in the intestines and brain, is important for the regulation of mood and cognition.[22] Marler et al., found an association between whole-blood serotonin levels and GI symptoms in ASD individuals.[23] These findings suggest that the gut plays an important role in the etiopathology of ASD.

Our knowledge of the microbiome has excessively expanded over the last few years. For example, researchers previously believed that the in utero environment was sterile.[24] However, recent work has shown that the infant gut is colonized by the microbiome of the maternal vagina, anus and skin during delivery and by the environmental bacteria to which the neonate is exposed during the postpartum period.[25] As demonstrated in recent studies, the placenta and the amniotic fluid are not sterile.[26] In addition, the microbiome in the first meconium of mice is not sterile, indicating that the microbiome colonizes the infant gut prior to parturition. Maternal factors, such as maternal diet and delivery mode, and postnatal factors, including antibiotics, breast-feeding, diet and host genetics, structure the neonatal microbiome in humans and animal models.[27] Furthermore, maternal obesity during pregnancy and gestational diabetes alter the gut microbiota and might be associated with ASD in humans.[28] The birth mode and antibiotics also shape the gut microbiota.[29] The composition of the microbiota of children who were treated with antibiotics during the first 3 years of life is less diverse in terms of both bacterial species and strains.[30] A population-based cohort study revealed the use of various antibiotics during pregnancy as a potential risk factor for ASD/infantile autism.[31] The early feeding pattern also influences the gut microbiota of infants and is associated with ASD. Breast-feeding for more than 6 months is associated with a lower risk of developing ASD.[32] Penn et al. studied infants with an older sibling diagnosed with ASD and found that breast-feeding might protect the infants against GI symptoms.[33] Infants who were delivered by Cesarean section (CS) are at higher risk of developing

ASD (odds ratio of 1.23) than infants delivered vaginally.[34] Children with ASD have a history of using significantly more antibiotics.[35] Thus, early life events that can alter the composition of the microbial community, such as delivery mode and antibiotic exposure, are risk factors for ASD.

Ayurvedic Perspective

Ayurvedic classical literature has broadly grouped the psycho social anomalies under the category of Unmada.[36] In addition to the etiology and pathogenesis, the literature vividly elaborates the signs, symptoms, and behavioral alterations in different psychiatric diseases. The concept of genetic defects (*Beejadushti*) either inherited from the parents or due to genetic shuffling and crossover during the stages of meiosis and fertilization (*swa karma klesham*) form the platform for all the cognitive and behaviour disorders in children.[37] Diet and regimen of the lady during pregnancy and mental stress has a direct influence in the psychological axis of the baby.[38] Auditory impulses experienced during that time is given much importance in shaping the psychological axis.[39] Gross impairment in above said circumstances leads to *Alpa Satwa* (feeble mindedness) of the individual.

Key role is attributed to the non-congenial dietetics (Virudhaahara) in precipitating clinical features. Unhygienic diet, intake of putrefied food, over eating, food intake in frequent intervals without considering the digestive capacity, food preparations with incompatible substances, excess use of artificial food additives, preservatives and flavonoids can be included under the non-congenial dietetics. These unhealthy dietetics can easily disturb the digestion and metabolism thereby disturbing the gut brain axis of the child.[40] Severe systemic illness is also attributed to derange the normal Agni and immune mechanism thereby making the individual prone to develop Psychiatric disorders.[41] Detailed analysis of the base somatic features of *Unmada* reveals that it is a disease with an inborn error in the digestive and metabolic capacity. Agni, the digestive fire is lacking a healthy genetic base in *Unmada*. So the baby is unable to have a proper digestion and metabolism which is evident from early infancy. Gut issues like bloated abdomen, colics, flatulence, constipation, irritable bowel etc are common clinical presentations. These digestive errors become more prominent with non-congenial dietetics. Direct clinical correlation with gut issues can be seen with dairy products like milk, chocolates, milk sweets, cashew nuts, pista, badam, ground nut and white flour. Psychological stress plays an important role in regulating the *Agni*.[42] Quality of *Agni* is influenced by the quantity as well as quality of food, compatibility of the food items, time and frequency of feeding and the psychological disposition of the child at the time of feed.[43-46] Any unexpected or unfavourable change in the living environment or caretakers is bound to increase the stress levels in these kids evident by their maladaptation tantrums. Usual accompaniments are temper tantrums, reduced span of attention, hyperactivity, irritability and disturbed sleep pattern.

Impaired digestive fire is unable to complete the proper digestion, resulting in the undigested or semi digested food in the *Koshta* (intestine) termed as Amasanchaya.[47] Among the somatic signs, gut dysbiosis - diarrhoea, constipation, bloating etc., goes hand in hand with the features of *Agnimandyam* (indigestion) which ends up in *Amasancayam* (accumulation of metabolic wastes) in the body.[48] This *Agnimandya* along with accumulated *Ama* is causing a local inflammation in the gut leading to increased permeability of the gut mucosal barrier (leaky gut syndrome). The accumulated *Ama* (semi digested or undigested macromolecules) in the intestine make its way into the systemic circulation and this condition is equated to *Dhathugathaama* in classical literature. [49] Ama entrapped or generated in the Dhatus are sure to hamper their functional integrity. These etiopathologies which happen in the early stages of brain developments has a negative impact on its functional maturity and coordinated activities. Dhatugathaama gets entrapped in the system as it can neither be utilized for bodily activities nor expelled as it is cannot find an easy way out of the body. So, classical references guide us to convert it into simpler molecules (*Pachana*) and couple with fatty preparations (*Snehana*) to pave its way back to *Koshta* for further elimination.[50] Repeated attempts with eliminatory procedures like *Vamana, Virechana* and *Vasthi* should be made to ensure their evacuation. The toxic by-products formed from these undigested food can act as toxins termed as *Amavisha* Entrapped *Ama* may be considered as a toxin, antigen or allergen to the body and Acharyas have rightly named it as Amavisha. [51] Treatment principles of *Dooshivisha* can also be sought of in managing these allergens/ toxins. [52] So, *Unmada* can be considered as a Psychological anomaly with a somatic base in the defective *Agni*.

Internal and external oleation (*Snehana*) along with fomentation followed by procedure based *Panchakarma* eliminatory therapies form the corner stone in the management of ASD.[53] Healthy mind is bound to accompany a healthy body. Correction of the *Agnimandya* with proper medications (*Deepana*), ensuring intake of congenial foods in optimum quantity and quality, avoidance of psychological stress by Yoga and breathing exercises, proper

exercise and play activities will help in improving the quality of intestinal microbiome thereby reducing the severity of ASD.[54,55]

Observational Study

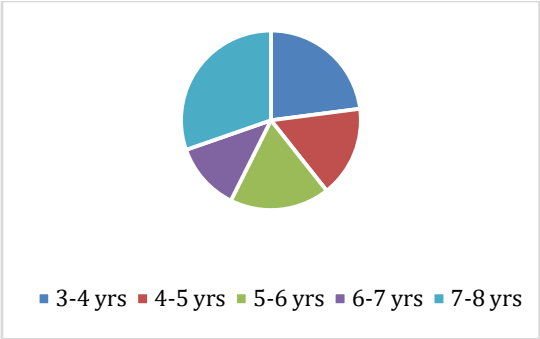
An observational study was carried out in the outpatient section of the Department of Kaumarabhrithya, Govt. Ayurveda College Hospital for Women and Children, Poojappura, Thiruvananthapuram in 122 children with ASD. Children between 3 to 8 years satisfying the DSM IV criteria with a childhood Autism Rating Score above 30 was included in the study. Socio demographic and clinical data related to *Agnimandya* and GIT abnormalities were collected.

Age distribution of participants

Table No. 1: Age distribution of participants

Variable	Total	
Age	**Number**	**Percentage**
3-4 yrs	28	23%
4-5 yrs	20	16%
5-6 yrs	22	18%
6-7 yrs	15	12%
7-8 yrs	37	30%
Total	122	100%

Fig No. 1: Age distribution of participants



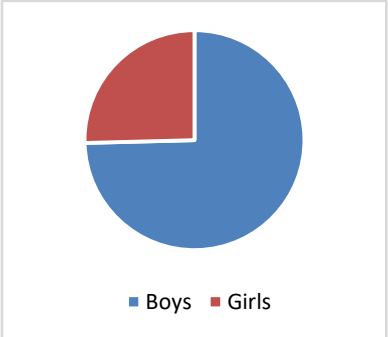
Age wise distribution of the participants showed 23 % of them were from 3 yrs, 16% from 4, 18% from 5 yrs, 12% from 6 yrs and 30% from 7 yrs. The higher contribution from upper age group point towards the necessity of popularizing Ayurvedic treatment among the public to facilitate early intervention.

Gender wise distribution of participants

Table No. 2: Gender distribution of participants

Variable	Total	
Gender	**Number**	**Percentage**
Boys	91	75%
Girls	31	25%
Total	122	100%

Fig No. 2: Gender distribution of participants



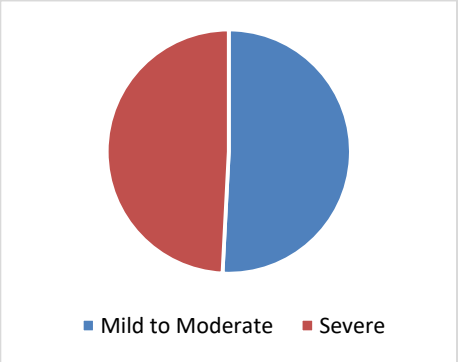
Gender wise distribution of the recruited patients depicted that 75% were boys and 25% were girls. Gender based data analysis came out with a male to female ratio of 3:1. Our study is in consistent with the meta-analysis, in spite of the fact that sex ratio of birth in Kerala reports 1:1.064 (M:F)

Distribution of participants as per Severity of Autism

Table No. 3: Severity of Autism in children

Variable	Total	
	No.	%
Mild to Moderate	62	51%
Severe	60	49%
Total	122	100%

Fig No. 3: Severity of Autism in children



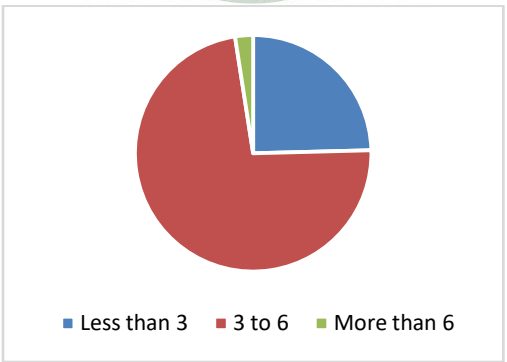
A case having a CARS2-ST score above 30 was recruited into the study. CARS2-ST score below 36.5 can be designated as mild to moderate Autism and above as severe cases. The study could ensure almost equal participation from both the groups.

Distribution of participants as per exclusive Breast feeding time

Table No. 4: Exclusive Breast feeding time

Variable	Total	
EBF months	Number	Percentage
Less than 3	30	25%
3 to 6	89	73%
More than 6	3	2%
Total	122	100%

Fig No. 4: Exclusive Breast feeding time



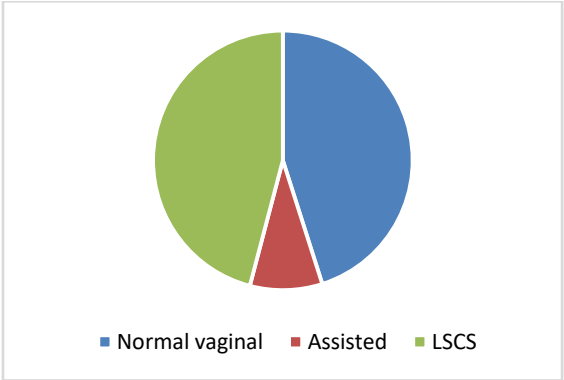
It was observed that 25% of mothers stopped exclusive breast feeding before 3 months. This finding is in accordance with the Meta-analysis reports stating that exclusive breast feeding may protect against the risk of developing ASD.

Distribution of participants as per Mode of Delivery

Table No. 5: Mode of Delivery

Variable	Total	
Mode of Delivery	Number	Percentage
Normal vaginal	55	45%
Assisted	11	9%
LSCS	56	46%
Total	122	100%

Fig No. 5: Mode of Delivery



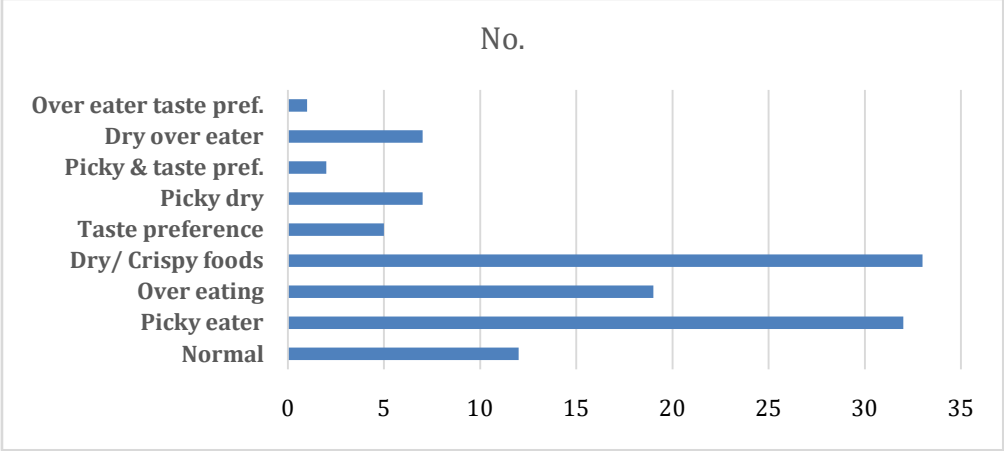
The world is currently witnessing an increase in the rate of caesarean sections which can be ascribed to many factors including socio-economic factors and personal preferences apart from the clinical indications. A community based cross sectional study conducted in Kerala has come up with a caesarean section rate of 37.7%. The rate of LSCS in the present study is much more (46%) than the expected level. This study confirms previous findings that children born by LSCS are more likely to be diagnosed as having ASD. However, the association did not persist when using sibling controls, implying that this association is due to familial confounding by genetic and/or environmental factors.

Distribution of participants as per eating habits

Table No. 6: Eating habits in participants

Variable	**Total**	
Eating habits	**No.**	**%**
Normal	12	10%
Picky eater	32	26%
Over eating	19	16%
Dry/ Crispy foods	33	27%
Taste preference	5	4%
Picky dry	7	6%
Picky & taste pref.	2	2%
Dry over eater	7	6%
Over eater taste pref.	1	1%
Dry & taste pref	3	2%
Picky, dry & taste pref	1	1%
Total	122	100%

Fig No. 6: Eating habits in participants



Children with autism frequently have significant eating difficulties with highly restricted range of food choices. The purpose of this data analysis was to get a parent survey of feeding patterns in children with autism to give a new perspective for both parents and professionals.

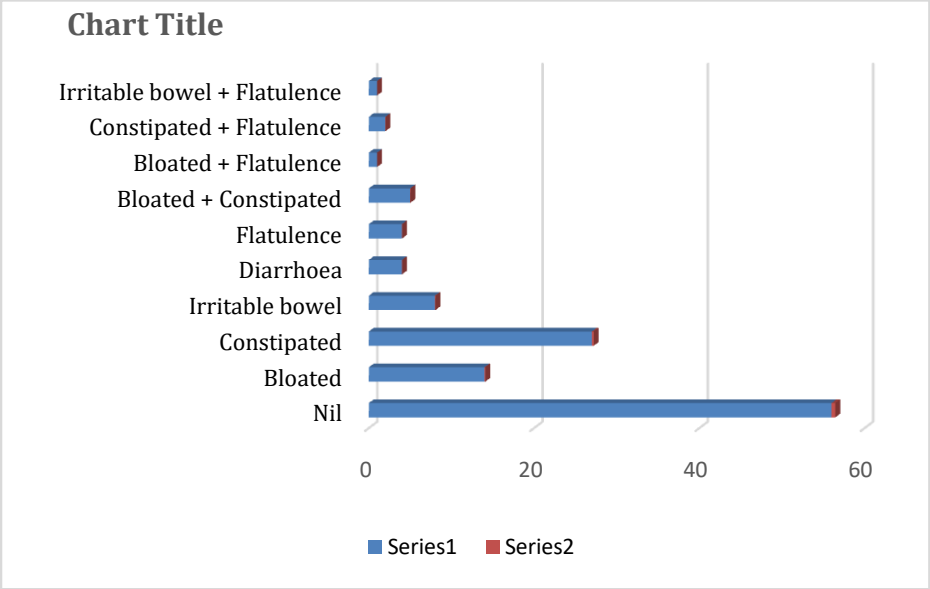
Picky eaters are very selective about what they eat. They are reluctant to eat, or even taste new foods. This result in children eating a limited variety of foods and this group comprises of 35%. Certain groups of kids, due to their sensory issues, are used to dry foods alone. They usually avoid wet side dishes and are fond of crispy food items. 42% of cases were under this group. Over eating was noted in 23%. Certain other group (10%) has special preference to particular tastes like sweet/ spicy.

Distribution of participants as per prevalence of Gut issues

Table No. 7: Gut issues in participants

Variable	**Total**	
Gut issues	**No.**	**%**
Nil	56	46%
Bloated	14	11%
Constipated	27	22%
Irritable bowel	8	7%
Diarrhoea	4	3%
Flatulence	4	3%
Bloated + Constipated	5	4%
Bloated + Flatulence	1	1%
Constipated + Flatulence	2	2%
Irritable bowel + Flatulence	1	1%
Total	122	100%

Fig No. 7: Gut issues in participants



Data pertaining to gut issues were collected from the informants. It was noted that 54% of the cases showed an evident disturbance in the digestive mechanism. Bloated abdomen was complained by 16% of cases, constipation by 28%, irritable bowel by 8%, increased flatulence by 7% and recurrent diarrhoea by 3%. Studies in this field states that, compared to normal children, those with ASD were more likely to have at least one frequent gastro-intestinal symptom. This data highlights the prevalence of digestive errors in these kids. Maladaptive behaviours correlate with gastro-intestinal problems, suggesting these comorbidities require attention.

CONCLUSION

This study emphasizes the role of defective gut microbiome in precipitating the socio behavioural problems in ASD kids. At present, there are no effective therapies for ASD. Accumulating evidences showed modulation of the gut microbiota might constitute a potential therapy in children with ASD. Correction of Agni and elimination of metabolic wastes by *Sodhana* therapies may prevent intestinal inflammatory diseases by regulating intestinal tight junction protein expression and barrier function.

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Cite this article as:
Roshni Anirudhan, M A Shajahan. Gut Brain Axis in Autism Spectrum Disorders - Ayurvedic Perspective. International Journal of Ayurveda and Pharma Research. 2018;6(11):29-38.
Source of support: Nil, Conflict of interest: None Declared

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