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Review

Nutrition Effect on Autism Spectrum Disorders

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ABSTRACT

Autism spectrum disorder (ASD) is a behavioral disorder that negatively affects the cognitive functions of the brain and other organs as well. One of these problems, digestive disorders, together with physiological mechanisms, affect the process in the brain and turn the disease into a cycle. Some mechanisms affect our digestive system positively or negatively depending on the type of food we consume. Research is being conducted on how disorders such as ASD, whose digestive system is sensitive, will affect their symptoms by supporting them with certain diets. Whether nutrition (Mediterranean diet, gluten-free/casein-free diet, ketogenic diet, special carbohydrate diet, low oxalate diet) is a part of existing treatment in ASD and its beneficial effects are examined. In this review, the effects of nutritional diets on ASD are discussed.

Keywords: Autism spectrum disorder, behavior, diet, nutrition.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that causes social communication and interaction problems, adaptation difficulties, speech impairment, repetitive movements, and interest in more than one area. Besides, adverse mental conditions (such as anxiety, depression), motor activity disorders (such as hypotonia), sleep problems, digestive problems, epilepsy, immune system problems, and mitochondrial dysfunction may also develop in the course of ASD. Risk factors include family history with ASD, having old parents, or having a mother who has been exposed to pesticides or certain medications, undergone infection, or have a chronic condition, such as diabetes, hypertension or obesity. While behavioral therapy treatment is widely used, some patients do not respond to it, and for them, drug therapy is used.[1] Behavioral therapy aims to teach new skills, reinforce these skills, and reduce unwanted behavior. 25 hours of therapy a week is recommended for early school age and preschool children.[1,2] Clinical studies have shown that behavioral therapy if done regularly for an extended period, improves cognitive ability, language skills and conformity. These effects have been reported to be clinically and statistically significant.[1,3]

There is an important link between behavioral disorders seen in ASD patients and gastrointestinal problems. It is possible to explain this link with the microbiota-gut-brain axis. While the brain controls the intestines in terms of movement and secretory functions, the intestines affect brain cognition. In ASD patients, this interaction between the brain and the intestines is disturbed. The relationship between digestive system problems seen in ASD and diets taken has been evaluated by multiple studies. The purpose of this review is to analyze these studies to have a better understanding of diet therapies on ASD patients. Moreover, we aim to also analyze diet therapies that have not yet been tried on ASD patients, although they can be useful considering the microbiota-intestinal-brain axis.

Microbiota is the colonization of microorganisms such as bacteria, archaea, fungi, viruses and protozoa.[4] Microbiota is found in all multicellular organisms studied to date, from plants to animals.

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Bacterial colonization begins immediately after birth, becomes similar to the adult microbiome between ages 1-3, and then remains mostly stable.[5,6] Microbiota is important in drug metabolism and protection against pathogens.[7-9] Intestinal microbial flora plays a role in appetite regulation, energy use, digestion and absorption of nutrients.[10,11] Disruption or imbalance of the microbiome is linked to several human diseases such as Inflammatory Bowel Disease, Cancer, Metabolic Syndrome, Obesity, Neurological Disorders.[12-19] There are important ways of interaction between the brain and the gut. One of the ways is the Vagus nerve of the parasympathetic system. The vagus nerve distinguishes between pathogenic and non-pathogenic bacteria, mediating signals that cause anxiogenic and anxiolytic effects, and acts as a communication path between the brain and the intestine.[20] Another way is the influence of bacterial species upon the immune system through the production of immune regulatory metabolites. An example of these metabolites is short-chain fatty acids, which are the end products of carbohydrate fermentation.[21-23] It has been suggested that short-chain fatty acids, namely Propionic Acid (PPA), Butyric Acid (BA), and Acetic Acid (AA) have various benefits to the host regarding weight control, lipid profile and colon health.[24] However, the accumulation of these acids (especially PPA) also affects the nervous system and it is linked to ASD.[25,26] Propionate attenuates the secretion of serotonin (5-hydroxytryptamine or 5'-HT) in the intestine. It acts as a neurochemical and has effects on the Central Nervous System function. These effects are thought to be associated with low levels of 5'-HT and dopamine in the brain.[27-29] Moreover, they may have a potential contribution to hyperserotonemia (excessive serotonin production) observed in children with autism.[27-29] Increased short-chain fatty acid concentration levels and increased levels of bacteria produced by short-chain fatty acids (Clostridia, Desulfovibrio, and Bacteroides)[30-32] seen in people with autism affect the brain by displacing with transporters or passive diffusion across the blood-brain barrier, which leads to the development of some ASD symptoms.[33] Although the effect of short-chain fatty acids on behavior is not exactly known, mitochondrial dysfunction (Krebs cycle) and epigenetic changes may be involved (Figure 1).[27]

5'HT is another important factor for social function and repetitive movements. 5'HT is involved in regulating neurodevelopment because it is produced in the intestine in high amounts and metabolized by the intestinal microbiota.[34] It has been reported that some bacterial species

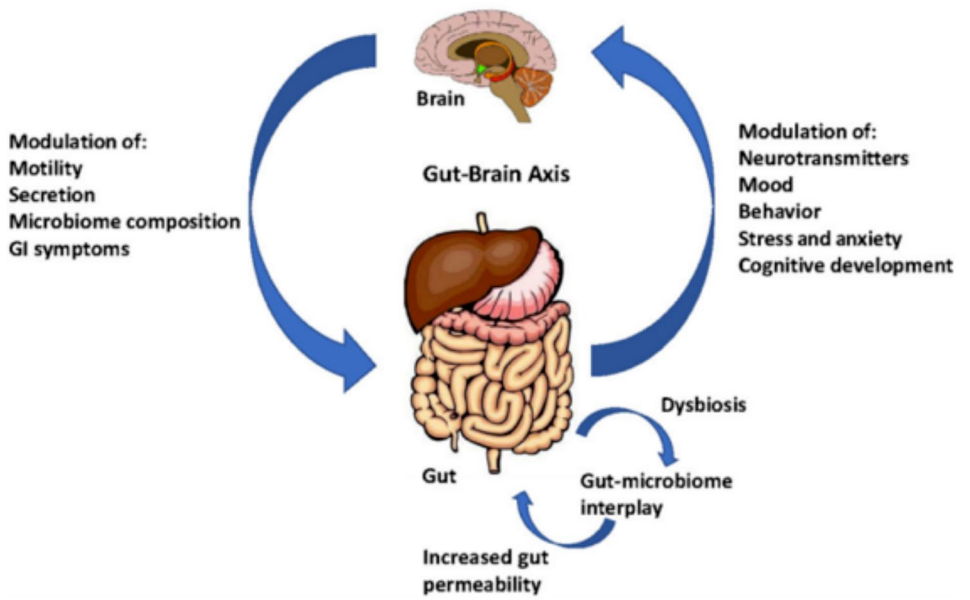

Figure 1. "A schematic representation of the interaction between the gut-brain axis. There is bidirectional communication between the gut-brain axis that can modulate GI and central nervous system functions. Gut microbiota that can be influenced by nutritional intervention plays an important role in governing this bidirectional signaling.[47]

GI: Gastrointestinal.

(Clostridium spp., Lactobacillus spp.) observed in the stool samples of children with autism change the function and metabolism of neurotransmitters, such as 5'HT and catecholamine and contribute to the symptomology with serotonergic system dysfunction.[34-39] It has been observed that approximately 30% of children with autism have high levels of 5'HT in their blood and platelets, and therefore 5'HT may be a candidate biomarker for the diagnosis of ASD.[36] Intestinal permeability can also cause 5'HT to enter the systemic circulation, causing elevated levels of 5'HT in the blood.[36,40-42] Increased 5'HT in the blood reduces the presence of peripheral tryptophan (the precursor of serotonin). Decreased tryptophan level is associated with the worsening of repetitive movements seen in individuals with ASD.[43,44] Also, the impairment of 5'HT inactivation causes increased 5'HT levels, and this is associated with intestinal inflammation, which may play a role in the inflammatory response.[45] On the other hand, dysbiosis (microbiota disruption) can reduce the number of amino acids absorbed from the diet, affecting the availability of tryptophan and serotonin synthesis.[46]

TOLL-LIKE RECEPTORS AND INFLAMED BOWEL

Toll-like receptors (TLRs) are expressed in a wide variety of immune cells. It plays an important role in innate immune responses. The intestine is a rich source of TLR ligands (compounds). Endogenous TLR ligands are released during disease, inflammation and tissue destruction processes. They have two important roles: being useful in providing tolerance and eliminating microorganisms. However, they can also cause chronic inflammation by increasing excessive immune responses. Large-scale studies have shown that TLR plays a role in dendritic cells and macrophages in patients with inflammatory bowel disease.[48,49]

THE RELATIONSHIP BETWEEN INTESTINAL INFLAMMATION AND FOOD

The intestine helps in the formation of the fundamental epithelial barrier. The surface area of this epithelial layer, which is connected by tight junctions, is thin and wide. The epithelial layer is constantly exposed to various food components, antigens, commensal microflora and pathogens. Most of the time, epithelial cells react to bowel movements, suggesting that the intestine is frequently in a controlled inflammatory state.[50-52]

It can be said that the amount of fiber intake in the diet, which is one of the factors affecting the epithelial layer, is important. Besides, foods such as fruits, vegetables, olive oil, and fish in the Mediterranean diet also strengthen intestinal health and the immune system.[53-55] Moreover, omega 3 is anti-inflammatory and can prevent intestinal inflammation.[56] Short-chain fatty acids that are produced by the fermentation of fiber in the intestines along with long-chain fatty acids and tryptophan metabolites also prevent inflammation.[54] Furthermore, refined sugar, complex carbohydrates (disaccharides and polysaccharides), high carbohydrate consumption and consumption of fast food-style foods increase the risk of intestinal inflammation.[57-66] In an epidemiological study conducted in Japan, the increase in total fat intake, animal fat intake, omega 6 unsaturated fatty acid intake, animal protein and milk protein intake have been associated with intestinal inflammation.[67]

MEDITERRANEAN DIET

Although there are no significant studies on the relationship between ASD and the Mediterranean Diet (MD), MD has been reported to be beneficial against the cardiovascular system, metabolism and mental diseases.[68-74] MD includes fruits and vegetables, legumes, nuts, cereals, olive oil, fish (moderate consumption), and alcohol (wine, etc.). Moreover, low intake of saturated fat, red meat and sugar is also involved in MD.[75]

In one study, the behavior of the offspring of 325 pregnant women was examined concerning the mother's degree of the rate of Adherence to the Mediterranean Diet (AMD). The offspring of mothers with high AMD were found to be less likely to have depression than the offspring of other mothers. Moreover, the likelihood of adverse behaviors in offspring of mothers with moderate AMD was found to be lower than the offspring of mothers with lower AMD. It was observed that the offspring of mothers with the lowest degree of AMD had more ASD behaviors than the offspring of other mothers with higher levels of adherence. It was found that the rate of AMD of the mother and the adverse behaviors of the offspring were inversely proportional. It was also concluded that the mother's AMD was not associated with externalization, dysregulation, or competence behaviors. Mother's high AMD has been associated with increased methylation of the SGCE/PEG10 locus in female offspring, reduced

depression, anxiety, atypical and ASD index criteria. Furthermore, the mother's high AMD has been associated with decreased methylation of the IGF2 and SGCE/PEG10 locus and increased methylation of MEG3 locus, which result in reduced adverse behavior, and increased social relations criteria, respectively.[76]

GLUTEN-FREE/CASEIN-FREE DIET

A protocol for gluten and casein-free diet involves excluding gluten-containing foods such as wheat, oats, rye, breadcrumbs, pasta, pastries, cereal baked goods, and casein-containing foods such as milk (including breast milk), yoghurt, cheese, butter, cream, ice cream and other dairy products. There are a limited number of studies in the literature regarding evidence of a gluten behavioral-free/casein-free diet (GFCFD).[77] From a health perspective, results show that GFCFD reduces the healthy bacterial population, increases opportunistic pathogens and has immunosuppressive properties.[78-80] Evidence in ASD shows that a gluten-free/casein-free diet reduces urinary peptides, improving ASD symptoms and behavior and decreasing symptoms of gastrointestinal discomfort. Inflammatory cytokines are released by casein and gluten, altering the intestinal epithelial barrier. These proteins and peptides are absorbed from the brain-intestinal barrier and affect the CNS. By removing gluten and casein in this diet, measurable behavioral changes have been observed in children with autism.[81,82] This diet is also recommended for people with allergic or allergic intolerance diagnosis other than ASD.[83,84] In other studies, it has been shown that this elimination diet may reduce fiber intake and thus lead to possible gastrointestinal problems.[83]

GFCFD restricts foods that contain gluten and casein. Though limited in the number of evidence in the literature, studies on GFCFD have shown positive results on ASD symptoms and behaviors, and it alleviated gastrointestinal symptoms. On the other hand, however, GFCFD studies have also shown some negative results such as suppressed immunity and a reduced number of beneficial bacteria. In a randomized controlled study with 80 people, it was observed that gastrointestinal symptoms alleviated and behaviors improved 6 weeks after the administration of GFCFD.[82]

In two other studies, the effect of the GFCFD diet on ASD was examined. A pilot study was conducted with 28 children and adolescents diagnosed with ASD, who received 3 months of gluten and casein on a normal diet followed by 3 months of GFCFD. The second study was conducted with 37 children and adolescents with ASD who have high urinary beta-casomorphin concentration, who received a normal diet containing gluten and casein for 6 months and GFCFD for 6 months. In both studies, no association was found regarding significant behavioral changes and urinary beta-casomorphin levels after GFCFD administration. However, it was concluded that more studies including placebo and blind options for at least 6 months or longer are needed.[85]

More studies are needed to resolve the contradictions regarding GFCFD results.

EXCESS OPIOID THEORY

The Gluten-Free/Casein-Free diet and the Opioid Excess Theory/Leaky Gut Theory are linked. Opioid Excess Theory has been suggested to be a metabolic disorder caused by the passage of opioid peptides produced by gluten-casein metabolism through the abnormally highly permeable gut. Allergens such as gluten disrupt the intestinal epithelial barrier function and thus result in an abnormally increased intestinal permeability. Opioid peptides are neuroactive peptides, which enter the bloodstream through a disrupted epithelial barrier and act on neurotransmission via opioid receptor binding, and thus affect the central nervous system. Removing gluten and casein prevents the increase of neuroactive peptides in the bloodstream, has an effect on neurotransmission in the brain and thus improves behavior.[40,86-88]

In an intestine with abnormal intestinal permeability, opioid peptide products formed as a result of gluten-casein metabolism pass into the bloodstream, where they bind to the opioid receptors. From there they are passed into the central nervous system and the neurotransmitters therein are affected. By restricting gluten and casein in GFCFD, the production of opioid peptides that will provide this transition is prevented.

KETOGENIC DIET

A ketogenic diet is a high fat, sufficient protein and very low carbohydrate diet. It is known to be effective in people resistant to anticonvulsant drug therapy, especially in epileptic patients.[70] It has also been reported that a ketogenic diet reduces the severity of the seizure and behavioral disorders in mild and moderate ASD patients.[89,90]

In one study, pregnant Swiss rats were administered valproic acid (VPA) (600 mg/kg) by intraperitoneal injection on the 11th day of their pregnancy. Two groups of 16 rats were formed. While the intervention group was exposed to valproic acid, the control group was not. Half of both groups received a ketogenic diet (KD) and the other half received a standard diet (SD). At the end of 70 days, a statistically significant result was found in the social behavior of VPA mice treated with KD compared to VPA mice treated with SD.[91]

In another study, male and female EL (mouse used in autism and epilepsy models) mouse model was studied with ASD and epilepsy behaviors. Three different diet treatments were tried for 3-4 weeks: 1 standard diet (SD), 2 ketogenic diets (KD) (one of the KD contains a higher fat ratio). In both groups fed with KD, it was observed that the time spent with a foreign mouse was increased in both female and male mice in the social recognition test. Especially in females fed a higher fat ketogenic diet, it has been observed that preference for new mice has increased and that self-care, which is a repetitive behavioral test, is significantly reduced in male mice. This reduction in self-care behavior was not a significant result in females.[92]

In a human pilot study, 30 children diagnosed with ASD were studied. The diet (medium-chain triglyceride 30%, 30% fresh cream, 11% saturated fat, 19% carbohydrate and 10% protein) was applied for six months. 40% of the children did not follow the diet or could not tolerate it. Only two children showed significant improvements on the Childhood Autism Rating Scale (CCDS), with the remainder showing mild to moderate improvement.[90]

In another study, a ketogenic diet (with a fat ratio of 1.5, a protein-carbohydrate ratio of 1) was given to a child with autism and epilepsy. Following the diet, several benefits have emerged, including reversing morbid obesity and cognitive impairment and improving behavioral traits. A few years after following the same diet, the child's CCDS score dropped from 49 to 17, which changed his condition from severe autism to non-autistic, and his IQ score increased by 70 points. Seizures also disappeared after 14 months in the diet.[93]

Ketogenic Diet (KD), which was primarily used to improve epilepsy seizures, must be high fat, sufficient protein and low carbohydrates. It has been observed that the KD in mice and rats increases social relationships and decreases repetitive movements. It has been also observed that the KD in children increases IQ scores and decreases the CCDS score. Increasing the number of studies for the effectiveness of KD on ASD will be beneficial in terms of determining the relationship between KD and ASD.

SPECIAL CARBOHYDRATE DIET

In the special carbohydrate diet (SCD), complex carbohydrates (starch products such as potatoes, disaccharides such as sucrose, etc.) and processed foods are restricted; vegetables, fruits, meat, eggs, nuts, legumes, honey, and foods with a monosaccharide structure (such as glucose) are included.[94] This is because complex carbohydrates, such as starch or disaccharides take longer to digest than monosaccharides. In SCD, it is aimed to prevent malabsorption of foods that are more difficult to digest, prevent the formation of undigested residual nutrients and, as a result, prevent the growth of pathogenic bacteria in the intestine. The protocol for SCD was developed for Celiac patients in the 1930s but was later applied in other intestinal diseases as well, such as Crohn's disease, Ulcerative Colitis, Diverticulitis, Chronic Diarrhea.[94-97] There are a limited number of studies that examined SCD for ASD. However, SCD is used to reduce nutrient absorption problems and inhibit the growth of pathogenic bacteria. Accordingly, gastrointestinal problems and behavioral problems caused by these problems are expected to be alleviated with SCD.

Special carbohydrate diet, which was primarily created to prevent complaints caused by intestinal problems, has also been tested in a limited number of studies in individuals diagnosed with ASD. The main purpose of using SCD in individuals with ASD is to alleviate the existing gastrointestinal symptoms. Consumption of processed food and complex carbohydrates in the SCD protocol is limited. In a study on SCD, a 12-year-old boy, who has been following a strict gluten-free/casein-free diet for 6 years with ASD was examined. While various and minor improvements were observed, the struggle with gastrointestinal problems continued. Also, tantrums, behavioral problems, and social-language problems continued. Subsequently, 6 months of SCD was used and impressive progress was made. The normal stool was observed on the 3rd day of the application of the SCD. Later, improvement in social behavior such as participating in classroom activities, language ability such as spontaneous speech or making complex sentences has been

observed. Promising developments such as skipping and spending more time in the classroom, creating special interests, spelling champions were noted. Gastrointestinal problems such as abdominal pain, gas and bloating have disappeared, and behaviors such as anxiety, fear and crying have started to be observed. Productivity also increased. In addition to SCD, the patient also received B12 injections, mixed supplements and social education. When goat yoghurt, cake and ice cream were given, negative reactions such as gastrointestinal problems and crying resurfaced. Finally, the mother of the patient stated that her son had a more participatory approach in crowded environments unlike in the past. SCD is thought to be a potent alternative to children or adults with Autism who do not respond adequately to the Gluten-Free/Casein-Free Diet.[94]

In another study, SCD protocol was applied to a 4-year-old child with both ASD and Fragile X Syndrome. It was observed that the patient could tolerate the diet well. SCD contributed to the child's growth; it reduced gastrointestinal symptoms and improved social behavior. More studies should be conducted on pediatric patients with these diagnoses to prove the effectiveness of the protocol.[96]

LOW OXALATE DIET

In individuals with ASD, some substances such as oxalate can disrupt neurological development and cause abnormalities in the nervous system.[98,99] Some metabolic disorders, including high levels of oxalate in blood serum, cause more intense clinical symptoms in these individuals. In a study, it was found that plasma oxalate levels of children with ASD were three times higher than the reference values (5.6 mmol/L vs 1.84 mmol/L) and their urinary oxalate levels were two and a half times higher. As a result, high concentration blood serum oxalate level and high concentration urine oxalate level may be one of the causes of ASD pathogenesis.[98,100]

The accepted value of oxalate intake for adults is 250 mg per day. This value increases up to 1000 mg in the Western diet. In individuals diagnosed with ASD, the daily intake value is limited to 40-50 mg. This limited value is allowed for beneficial foods that are rich in oxalates.[98,101] These foods are spinach, beets, cocoa, black tea, figs, green apples, black grapes, kiwi, tangerines, strawberries, oats, wheat, millet, peanuts, cashews, hazelnuts, almonds and blueberries.[98,102] Supporting supplements such as vitamins A and E, arginine, taurine, glucosamine, glutathione, thiamine, magnesium, coenzyme A, citrate, magnesium, calcium and zinc are also recommended in a low oxalate diet.[98]

CAMEL MILK

Camel milk has an extremely low-fat content of 2 per cent, and its main fat content consists of long-chain polyunsaturated fatty acids essential for brain development. Its low-fat content gives camel milk a watery taste.[103] When we examine camel milk in terms of protein content, it is similar to cow's milk (3.2%). But the beta-lactoglobulin and beta-casein allergens found in cow's milk are absent in camel milk. Since these two components are necessary for cheese making, cheese cannot be made from camel milk. Opioid (casomorphin) formation in autistic children occurs when these two caseins are broken down incorrectly.[103-105] The deficiency of these caseins in camel milk prevents the development of autism symptoms.[103] Camel milk contains protective proteins and bacterial enzymes involved in the immune system. These enzymes have antibacterial and antiviral properties.[103-105] Camel milk also contains insulin.[106] Although camel milk contains similar percentages of lactose to cow's milk, people with lactose intolerance can drink camel milk without adverse effects. Besides, camel milk is a rich source of vitamin C, calcium and iron. Being rich in vitamin C ensures a low pH level. This way, iron and calcium are better absorbed.[103]

The antibodies of camels are also unique because of their heavy chain antibody structure without the presence of a light chain antibody structure. These unique antibodies have a great advantage over human antibodies because they can completely neutralize enzymes and are active against many viral diseases. IgM, IgG, IgA and IgD antibodies have been detected in camel serum.[107] The fact that camel antibodies have sizes as small as only one-tenth of human antibodies is also useful for the treatment of human diseases.[108] Their small size can have a positive effect on people suffering from a weak immune system.[109,110] This can be explained as follows: Immunoglobulins pass from the blood of the camel to the milk and into the bloodstream of the person who consumes the milk. Antigens absorbed from milk penetrate the tissues and reach the antigens. The general positive mechanism of action of camel milk in autoimmune diseases is explained in this way.[103]

Although ASD has many different manifestations, it firstly causes symptoms in the digestive

system and secondly in the nervous system. Faulty breakdown of the casein causes the formation of the opioid casomorphin, endangering the immune system. Subsequent cognitive and behavioral changes can eventually result in brain damage.[103]

It is thought that autism may be associated with autoimmune disease. A decrease in the severity of behavioral and cognitive symptoms is observed as a result of intravenous immunoglobulin therapy (IVIGT).[103,111] Likewise, similar results are seen in the consumption of camel milk. The consumption of camel milk plays a therapeutic role like IVIGT, suggesting that there may be a link between milk and the immune system. Complete recovery has been observed in children younger than 10 years with IVIGT or camel milk treatments. In children older than 15 years, it was observed that similar symptoms returned as a result of the discontinuation of IVIGT or camel milk treatments. When cow's milk is excluded from the diet, symptoms are suppressed, however, the reversal of disease is not seen. It is thought that camel milk contributes to the prevention of brain damage at an early age, as parents observe that the positive response in young children is higher than in older children.[103]

The hypothesis of morphine-like symptoms caused by the abnormal breakdown of milk casein in autistic children was approved in experimental animals. Rats were injected with beta - casomorphin - 7.[103,112] Rats who watched the bell ringing before being injected were not interested in the bell ringing after the injection. When the brain tissues of experimental animals were examined, it was observed that beta - casomorphine - 7 was located in thirty-two different brain regions responsible for hearing, vision and communication.[103]

A double-blind randomized study was conducted to examine the effect of camel milk consumption on oxidative stress biomarkers in autistic children. 60 children with autism were involved in this study. These children were randomly assigned to the raw camel milk drinking group, the boiled camel milk drinking group, or the cow's milk group, which was the placebo. Each child regularly consumed 500 ml of milk daily for two weeks. In groups consuming camel milk, plasma glutathione, superoxide dismutase, and myeloperoxidase levels increased and Childhood Autism Assessment Scale (CAAS) improved. These findings support that camel milk can contribute to improving autistic behaviors by reducing oxidative stress, which plays a role in autism.[113]

RESULT

Nutrition, which is among our basic physiological needs, is important for all people. Individuals with systemic symptoms such as ASD should pay attention to their diet in order not to worsen their current condition and increase their quality of life. Various dietary interventions are tried to alleviate the symptoms of ASD. Nutrition plays an important role in healing gastrointestinal problems that patients with ASD suffer from. Several dietary protocols have been created by considering the microbiota-gut-brain axis and they have been mentioned in this paper. Studies that examine the effect of the Mediterranean Diet, Gluten-Free/Casein-Free Diet, Ketogenic Diet and Special Carbohydrate Diet, Low Oxalate Diet, Camel's Milk on ASD and neurodevelopmental disorders are available. These studies, however, are not enough to prove the effectiveness of these diets. Studies on the feasibility of various dietary modifications or combinations may be also increased. Accordingly, individual-specific arrangements can be made on existing dietary protocols. Overall, more studies are needed for proving the effectiveness of the aforementioned diets in individuals with ASD.

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