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Review Article

Gut-Brain Axis and Ketogenic Diet in Autism

Flávio Eduardo Dias Araújo Freitas[1], Ludmila Lizziane de Souza Lima[2,1], Karine Luana de Morais[3], Carlos Eduardo de Freitas Jorge[4], Giselle Foureaux[1]*

[1]*Department of Morphology, Federal University of Minas Gerais, Belo Horizonte, Brazil*

[2]*Department of Food Microbiology, Federal University of Minas Gerais, Belo Horizonte, Brazil*

[3]*College Anhanguera, Contagem, Brazil*

[4]*Angiogold Institute of Education and Research, Brazil*

***Corresponding author:** Giselle Foureaux, Institute of Biological Sciences, Department of Morphology, Federal University of Minas Gerais, Avenida Presidente Antônio Carlos, Pampulha, Belo Horizonte, Minas Gerais, Brazil.

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Abstract

Autism is a neurodevelopmental disorder characterized by behavioral modulation, manifesting as qualitative impairments in social communication, social interaction, stereotyped repetitive behaviors, and food selectivity. It is estimated that 1 in every 36 children is diagnosed with autism globally, with factors such as changes in diagnostic methods and environmental influences—including diets high in sugars and ultra-processed foods—contributing to this increase. This review article explores how the ketogenic diet may influence the gut-brain axis in individuals with autism. Animal studies indicate that an unbalanced diet can adversely affect brain development, contributing to symptoms of Autism Spectrum Disorder (ASD). Maternal obesity is highlighted as a factor that can lead to fetal brain inflammation, potentially resulting in characteristics associated with autism. The focus of this review is to demonstrate the significance of nutrition during child development. Nutritional factors, such as deficiencies in essential fatty acids and diets high in sugars, are associated with increased brain inflammation and reduced neuroplasticity. Conversely, a balanced diet can promote neurological health. The ketogenic diet, which consists of high fat and low carbohydrate intake, has shown potential benefits for individuals with ASD, including improvements in brain function and behavioral. This review suggests that nutritional interventions may provide new avenues for treating ASD by considering the complex interactions between diet, gut microbiota, and mental health. In summary, the document concludes that the ketogenic diet crucial roles in mental health and neurological development, presenting promising areas for future research and interventions in the context of autism.

Keywords: Autism spectrum disorder (ASD), Ketogenic diet, Gut-brain axis, Dietary interventions, dietary Interventions

Introduction

In 1943, *Leo Kanner* [1] defined Autism Spectrum Disorder (ASD) as an innatecondition characterized by difficulty in establishing emotional contact normally expected in the population [1]. Since the initial discovery of ASD until the present day, social deficits and lack of motivation for social reciprocity have been essential components for the diagnosis of ASD [2]. Autism is a disorder

characterized by behavioral modulations, which is manifested by qualitative impairments in social communication, social interaction, stereotyped repetitive behaviors and food selectivity [3] In addition, in recent decades there have been significantadvances in the diagnosis of autism, aiming at a more precise delimitation through the ICD-10 (International Classification of Diseases, 10th edition) [4] and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, www.dsm5.org) [5]. Lately, we have seen an increase in the number of children diagnosed with ASD [6]. According to the World Health Organization in 2023, it is estimated that one out of every 100 children is diagnosed with autism globally. However, according to estimates from the Centers for Disease Control and Prevention's Developmental Disabilities and Disease Control Monitoring Network, approximately 1 in 44 children is diagnosed with an ASD [7]. This increase has led several researchers to investigate the phenomena underlying this rise in diagnoses of this disorder. Would external factors such as food, environment, socioeconomic conditions, or changes in diagnostic methods be responsible for this trend? Recent studies proposed to investigate possible factors that contributed to the increase in ASD worldwide, and the following elements were identified: a change in conceptualization, moving from a categorical central condition to a broader spectrum; changes in diagnostic methods; and the inclusion of children with disorders such as attention deficit hyperactivity disorder and Tourette's syndrome [8]. While changes in diagnostic patterns have boosted diagnosis rates in recent years, we recognize that other external factors can play a significant role in the development of the disorder.

One of the external factors that deserves consideration is a diet rich in sugars, carbohydrates, ultra-processed products and trans-fat. In the 2007 study by Kim and colleagues, a significant increase in overweight and obesity rates was observed among women of reproductive age [9]. Overweight/obesity during pregnancy is associated with the emergence of several comorbidities, such as gestational diabetes, type 2 diabetes and metabolic syndrome [10]. In recent years, there has been a significant increase in the number of children diagnosed with mental, behavioral, and neurodevelopmental disorders. It is estimated that 15% of children aged 2 to 8 years have one or more neurodevelopmental disabilities. Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) have emerged as particularly significant public health concerns. While genetic factors play a crucial role in the etiology of ADHD, ASD, and related conditions, non-genetic influenceson these neurodevelopmental disorders are not yet fully understood.

Understanding the factors contributing to ADHD, ASD, and children's neuropsychological development is essential for identifying solutions that improve child mental health outcomes and reduce the prevalence of these conditions in the population. Prenatal exposure to environmental toxins, stress, and inadequate nutrition has been associated with neurodevelopmental outcomes in children. It is important to note that the increase in the prevalence of neurodevelopmental problems has been accompanied by a rise in the prevalence of obesity in society. This parallel, along with preclinical data linking ultra-processed diets that are high in calories, but low in nutrientes and pregestational obesity to improper brain and behavioral development in offspring, suggests a potential connection between these two recent trends. Several studies have explored the direct impact of consuming an unbalanced diet rich in fast foods during pregnancy, which can result in changes in brain development and contribute to neurodevelopmental disorders such as ASD [11], Attention Deficit Hyperactivity Disorder (ADHD) [12,13], schizophrenia [14,15], anxiety and depression [16]. Consequently, attention to maternal weightstatus, whether pregestational weight or excessive gestational weight gain, has gained relevance concerning children's neurodevelopmental outcomes.

The gut-brain axis hypothesis proposes that the nutritional environment from the prenatal stage through early childhood can critically impact cognitive functions and susceptibility to ASD in genetically predisposed individuals [17]. This hypothesis suggests that nutritional influences during gestation and early postnatal development can shape neurological outcomes and increase the risk for the manifestation of ASD symptoms in those with a genetic vulnerability. Various animal studies have been conducted to explore how nutritional factors might affect the development and expression of ASD symptoms, seeking to clarify the role of dietary components in the pathophysiology of this neurodevelopmental disorder [13]. One prominent example is the suggestion that maternal obesity could be a contributing factor to fetal brain inflammation, which might later manifest as ASD traits. Additionally, the nutritional balance of the diet during pregnancy, including the presence of essential Polyunsaturated Fatty Acids (PUFAs) [18], is linked to cognitive processes such as memory and learning. Insufficient levels of these critical nutrients during pregnancy have been associated with potential cognitive deficits if not corrected early in developmental stages. Beyond nutritional considerations, research has shown that individuals with ASD often present with increased activation of microglial and astrocytic cells, as well as severe chronic inflammation in multiple brain regions, which may be closely related to the emergence of ASD symptoms [19]. Experiments with germ-free mice haveillustrated that these animals display impaired microglial development and inadequate myelination, highlighting the essential role of a healthy gut microbiota in normal brain development [20]. These findings are connected to changes in cytokine and neuropeptide levels, as well as deficiencies in microbiota-derived substances such as short-chain fatty acids and lipopolysaccharides. The bidirectional nature of gut-brain communication underscores that alterations in central nervous system function can affect gut health, while disturbances in gut microbiota can, in turn, impact brain function and behavior. This understanding of gut-brain interactions provides new potential targets for therapeutic approaches aimed at managing ASD and related disorders.

An issue of utmost importance for health is the early diagnosis and effective treatment of patients with ASD. However, due to the complex and heterogeneous nature of ASD, our current understanding of its pathogenesis remains insufficient [21]. Given this complexity, various authors have debated a wide range of approaches to provide an accurate diagnosis. These strategies encompass both behavioral analysis [22]. *(Carty, 2024)* and the consideration of the neurobiological context, which includes multiple perspectives. Among these, functional connectivity and the anatomical structure of the brains of individuals with Autism Spectrum Disorder (ASD) stand out [23] along with the variations that can be observed among them. Currently, there is an increasing search for strategies that allow for the differentiation of these behaviors, aiming for a more accurate diagnosis of ASD. Recent research has revealed evidence of the frequent association between ASD and a variety of conditions, including irritability, aggression, self-injurious behaviors, Attention Deficit Hyperactivity Disorder (ADHD), anxiety obsessive-compulsive disorder, gender dysphoria, mood disorders, suicide, substance use disorders, catatonia, psychosis, and schizophrenia spectrum disorders [24]. The significant difficulty in obtaining an accurate diagnosis of ASD arises from the fact that many behavioral and psychiatric disorders tend to overlap with the core characteristics of ASD [25]. This overlap creates considerable challenges, further complicating diagnostic precision. Given the wide diversity and the association of ASD with various conditions, we are on the brink of a significant advancement in knowledge. Although there are scales linked to the DSM-5, it is essential to acknowledge that these assessments are quite subjective. Various studies have demonstrated the use of biomarkers, with the most frequently investigated being cytokines, growth factors, measures of oxidative stress, neurotransmitters, and hormones. These investigations also include neurophysiological analyses (such as electroencephalograms and eye tracking), neuroimaging (like fMRI), and other physiological measures [25-28]. However, as evidenced in the article, the biomarkers examined across multiple studies have produced predominantly inconsistent results, revealing a genuine "replication crisis." This situation underscores the urgent need for a more rigorous and standardized approach in biomarker research to enhance diagnostic accuracy and interventions for individuals with autism [29]. This complexity highlights the importance of a careful and comprehensive assessment to ensure that individuals receive appropriate and effective treatment. A meticulous approach is essential for differentiating symptoms and ensuring that each patient has access to the necessary support for their development and well-being. Nutrition is now recognized as one of the possible risk factors for the neurodevelopmental diseases [30]. Knowing the dietaryhabits and lifestyles can exacerbate or improve the symptoms of the disease by modulating inflammation, interacting with cells and the intestinal microbiota. The objective of this review was to provide an update regarding the role of the intestinal microbiota in ASD.

Nutritional Importance in the Neurological Development

According to epidemiological research, the prevalence of Autism Spectrum Disorder (ASD) has been increasing globally. This growth is particularly pronounced in developed countries, where diagnosis rates continue to rise year after year. In contrast, in developing nations, the prevalence appears to have decreased, a phenomenon that can be attributed to a lack of resources and challenges in accessing adequate diagnostic services [31-33]. The rising prevalence of ASD in economically advanced countries can be explained by broader access to medical resources and the implementation of improved diagnostic tools and criteria [31-33]. This enables earlier identification of cases, preventing them from being misdiagnosed as other disorders and neuropathologies. This situation reflects an evolution in available diagnostic procedures, contributing to greater awareness and understanding of ASD. According to the literature, there is evidence that points to the crucial role of maternal nutrition in the neurological development of the fetus during the gestational period, which can influence both positively and negatively the etiology of autism [34]. In the 17th century, philosopher John Locke proposed that a baby's mind is a "blank slate", that is, a blank slate which is filled in by experiences throughout life. This theory has been accepted for many years, but several studies have shown the opposite, that this modulation occurs even before the baby is born, that is, the experiences and perceptions are acquired by the fetus in the womb of its mother [35]. The experience acquired in the womb, which we can call fetal programming, is transferred from the mother to the fetus through environmental factors. These factors can cause behavioral and physiological changes even before birth, filling in the "clean slate" of the fetus [36]. Among the behavioral and physiological changes that occur in the fetus during pregnancy and which can have long-term consequences, we can list low birth weight, high cortisol levels and a greater risk of developing chronic diseases such as hypertension and diabetes in adulthood [37]. According to some researchers, the intrauterine environment can modulate the physiological and behavioral programming of the fetus, which can lead to a predisposition to diseases in adulthood [38]. This theory, called fetal programming, is still under development, but the most accepted hypothesis is that these changes in the intrauterine environment are a way to protect the fetus from the environment it will encounter at birth [36-38].

The experience of the fetus in the intrauterine environment can modulate several physiological functions, mainly in the brain function. These alterations can trigger several individual differences, which can contribute to the development of behavioral dysfunction and risk of chronic diseases throughout life [38]. Such alterations come from the interaction of the gene with the environment in which the offspring is found and it account for most of the variations caused by the differences exposed by

each individual. They can lead to changes in DNA structure and chromatin functionality, resulting in a change in gene expression. [38]. Epigenetic changes, resulting from physical modifications of the DNA molecule and chromatin function, are responsible for regulating the operation of the genome and may have an impact on the development of brain structure and function [38]. Currently, we know that a variety of nutritional factors significantly contribute to alterations in the central nervous system [39]. For example, deficiencies inomega-3 fatty acids, vitamin B12, and folic acid can lead to cognitive and behavioral dysfunctions. Additionally, diets high in hydrogenated vegetable oils and sugars have been associated with increased brain inflammation and reduced neuroplasticity. In contrast, a balanced diet rich in antioxidants, such as fruits and vegetables, rich in protein and good sources of fat can promote neurological health and protect against cognitive decline [40]. Furthermore, the ketogenic diet, characterized by low carbohydrate intake and high consumption of healthy fats, has demonstrated benefits at the cerebral level, including improved mitochondrial function and a reduction in epileptic seizures in individuals with refractory epilepsy [41]. Another extremely important external factor for the propensity for alterations in the central nervous system is the consumption of alcoholic beverages during pregnancy, which can damage the central nervous system of the fetus, leading to Fetal Alcohol Syndrome (FAS). FAS is a disorder that can cause a range of health problems, including developmental delay, learning difficulties, behavior problems and physical defects [42]. The nutritional health of the mother is essential for the healthy development of the fetus [43]. When the mother is not adequately nourished as a result of drinking alcohol or due to alcohol consumption, the fetus may not receive the nutrients it needs to grow and develop properly [43]. This can lead to a number of health problems, including low birth weight, prematurity and birth defects [43].

The mother's diet plays a crucial role in shaping children's food preferences and selectivity. Research indicates that exposure to diverse flavors and aromas during pregnancy and breastfeeding can significantly influence future food preferences. A study by [44] found that the variety of flavors in breast milk is linked to greater acceptance of solid foods when the child begins complementary feeding. Consequently, a varied and nutrient-rich diet during pregnancy and lactation can encourage a broader acceptance of different foods, thereby reducing food selectivity and fostering a more balanced and varied dietary pattern [44]. The highly selective eating behaviors seen in children with ASD can be a significant factor in exacerbating autism symptoms. This food selectivity, which is often driven by the texture, smell, taste, and color of foods, results in very restrictive diets that may potentially worsen the symptoms of the disorder and make treatment more challenging [45]. Currently, there are a variety of pharmacological forms used to improve behavior in patients with autism, including FDA, approved atypical antipsychotic drugs such as Risperidone and Aripiprazole [46]. However, several clinical studies have shown that these drugs can carry adverse risks [47]. Due to the lack of effective and safe treatment options for autism, there is a growing need to investigate new interventions. In this context, several studies have been conducted in recent years with the aim of establishing possible relationships between autism and the nutritional status of patients, based on these patterns. A dietary approach has been widely adopted as an effective and safe treatment to improve neurodevelopmental disorders [48]. In particular, the Ketogenic Diet (KD) has gained prominence, consisting of a low- carbohydrate, moderate-protein, and high-fat diet [49].

Ketogenic Diet (KD) of Autism Spectrum Disorder

The KD is characterized by a specific distribution of macronutrients that aims to induce and maintain a state of ketosis, where the body uses ketones, derived from fats, as its main source of energy. In a typical ketogenic diet, approximately 70% to 80% of daily calories come from fats [50]. This high percentage of fats is essential for the continuous production of ketones, since, in the absence of sufficient carbohydrates, the body resorts to stored fats for energy [51]. In this diet, protein intake is moderate, representing approximately 15% to 25% of daily calories. This level of protein is sufficient to meet the body's needs without interrupt ketosis [52]. Reduced carbohydrate intake is the most striking feature of the ketogenic diet, with less than 5% to 10% of daily calories coming from this macronutrient. Generally, this translates into a daily carbohydrate intake of about 20 to 50 grams [52]. When the reduction in carbohydrates is not as pronounced as in the KD, but the level of this macronutrient is still lower than that recommended by conventional nutritional guidelines, we call it a low carbohydrate diet, or low-carb diet. This dietary strategy has gained popularity on social media in recent years as an effective strategy for weight loss and improving metabolic health [53]. Whose the main characteristic focuses on reducing carbohydrate consumption, prioritizing the intake of proteins and healthy fats. Although there is no consensus on the exact amount that should be consumed, most versions of the diet recommend limiting carbohydrate intake to less than 130 grams per day, in contrast to a standard diet, which may include 250-300 grams or more of carbohydrates daily [54]. Carbohydrate reduction aims to minimize blood glucose spikes and insulin response, promoting more efficient energy use. Studies suggest that a low- carb diet can bring several health benefits, which go far beyond weight loss, including reduced triglyceride levels, improved glycemic control, and decreased insulin resistance [55]. These effects are particularly beneficial for people who are overweight, obese, and have type 2 diabetes [55].

The KD has been shown to be more effective for behavioral improvement compared to the low-carb diet due to several factors related to its metabolic and neurochemical impact [56]. One of the

main characteristics of the ketogenic diet is its ability to induce a state of ketosis, in which the body uses ketones, derived from fat burning, as its main source of energy [57]. This state not only favors weight loss but can also positively influence brain function. Ketones are known to be a more efficient energy source for the brain compared to glucose, which can result in improvements in mental clarity, focus, and, consequently, behavior [58]. In addition, the ketogenic diet has been associated with reduced inflammation and control of blood glucose levels, factors that can directly impact mental health and emotional well-being [59]. Studies indicate that decreasing insulin spikes and stabilizing glucose levels can help regulate mood and reduce anxiety, contributing to better behavioral health [59]. On the other hand, the low-carb diet, although it also reduces carbohydrate intake, does not necessarily induce ketosis at significant levels. This means that the neurochemical benefits associated with ketones may not be as pronounced in this approach, limiting its effectiveness in improving behavioral aspects. Initially applied to epileptic patients, KD has been shown to significantly reduce epileptic seizures [60]. The Ketogenic Diet (KD) is a dietary plan characterized by high proportions of proteins and fats, and low carbohydrate content, which contributes to improving energy metabolism. KD acts by increasing Adenosine Triphosphate (ATP) levels, together with associated enzymes, modulating mitochondrial metabolic pathways and resulting in improved mitochondrial biogenesis. The ketone bodies generated by KD are produced from the conversion of acetyl-CoA under the influence of d-β- hydroxybutyrate dehydrogenase, acetoacetate succinyl-CoA transferase and acetoacetyl- CoA- Thiolase. These ketone bodies, including β-hydroxybutyrate, acetoacetate and acetone, are used as fuels in specific physiological conditions, such as prolonged fasting or starvation, being able to cross the Blood-Brain Barrier (BBB) and serve as fuel for the brain. Furthermore, ketone bodies have the ability to act as neuroprotectors of the central nervous system, as, in addition to the generation of ketone bodies, they also have the secondary effect of decreasing the production of Reactive Oxygen Species (ROS) by mitochondria.

Studies support the idea that KD promotes alteration of neural cell metabolism, using ketone bodies as an energy source for the brain [61,62]. This metabolic shift is thought to be responsible for the benefits seen on the ketogenic diet [63]. Early case reports in a pilot study involving 30 individuals with autistic behavior suggest that the ketogenic diet may be an effective strategy in the treatment of ASD [49]. Furthermore, in a clinical trial involving the evaluation of 45 children with ASD, it was found that the ketogenic diet was able to significantly improve the manifestations of clinical symptoms associated with ASD [64]. Evidence suggests that correlations between the beneficial effects of the ketogenic diet and the improvement of autism symptoms [65] may be related to the modulation of the intestinal microbiota, which in turn contributes to the homeostasis of the central nervous system [66].

Furthermore, the ketogenic diet influences the dynamics of neurotransmitter systems, particularly by modulating GABAergic and glutamatergic signaling GABA, or gamma-aminobutyric acid, is the principal inhibitory neurotransmitter in the central nervous system, synthesized through the decarboxylation of glutamate, the primary excitatory neurotransmitter [67]. The physiological pathway of GABA involves the conversion of glutamate to GABA via the enzyme Glutamate Decarboxylase (GAD), which catalyzes the removal of the carboxyl group from glutamate, resulting in the formation of GABA [68] *(Petroff, 2002)*. GABA predominantly acts through its receptors, GABA_A and GABA_B, which mediate synaptic inhibition and modulate neuronal excitability. In individuals with ASD, studies have revealed significant alterations in glutamatergic homeostasis, evidenced by abnormalities in the levels of proteins and mRNAs that regulate glutamatergic neurotransmission in the cerebellum, a brain region crucial for motor coordination and sensorimotor integration [69]. This imbalance can result in heightened neuronal excitability and exacerbation of ASD symptoms [69]. The KD, characterized by high intake of medium-chain fatty acids and severe carbohydrate restriction, induces the production of ketone bodies, including Beta- Hydroxybutyrate (BHB) [70]. BHB exerts a direct effect on excitatory neurotransmission by modulating glutamate receptor activity, specifically through the inhibition of NMDA (N-methyl-D-aspartate) receptors, which are key mediators of neuronal excitability and synaptic plasticity [71]. This inhibitory effect leads toa reduction in the frequency and severity of seizures, a symptom frequently addressed in ASD therapy [72]. Additionally, KD promotes an increase in GABA levels in neurons and astrocytes. BHB can modulate GABA_A receptor function, enhancing its inhibitory effects through potentiation of GABA's action on its receptors, thereby promoting greater neuronal stability [72]. The KD also reduces the degradation of GABA in astrocytes, contributing to increased GABA levels and a more balanced neurochemical environment.

Studies have shown that children with ASD often exhibit reduced GABA levels in sensory- motor regions, which correlates with tactile deficits and inferior sensory performance compared to neurotypical children [73]. Furthermore, reductions in GABA in the auditory cortex have been associated with abnormal neuronal circuit maturation, as evidenced by advanced imaging techniques such as Magnetoencephalography (MEG) and edited Magnetic Resonance Spectroscopy (MRS), which reveal significantly lower GABA concentrations and abnormal neuronal activity patterns in ASD patients [74]. In summary, the KD may serve as an effective therapeutic intervention for ASD by modulating neurotransmitter systems. Through the enhancement of GABA levels and the regulation of glutamatergic neurotransmission, KD has the potential to restore neurochemical balance in the brain and contribute to the improvement of behaviors associated with ASD. Another role of the KD in improving ASD symptoms concerns the reduction of inflammation, which is other risk factor ASD. For instance, pregnant mice were injected with Double-Stranded RNA (dsRNA)

poly (I:C) to simulate a viral infection, and the offspring of these mice exhibited ASD-like behavioral phenotypes [75]. Additionally, patients with ASD show evidence of aberrant inflammation in the central nervous system. Specifically, pro-inflammatory cytokines and chemokines, such asinterleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and Monocyte Chemoattractant Protein-1 (MCP-1), are found at abnormal levels in both brain tissue and Cerebrospinal Fluid (CSF) samples from individuals with ASD [76]. These cytokines activate the inflammatory response through the nuclear factor kappa B (NF-κB) signaling pathway, which plays a pivotal role in the regulation of inflammation and immune responses. Young and colleagues discovered that NF-κB protein was hyper-expressed in mature microglia in brain samples from ASD patients, indicating that immune activation is present in the brains of individuals with ASD. Additionally, ASD patients exhibited significantly higher levels of eight inflammatory cytokines in plasma compared to neurotypical controls. Individuals with ASD also show a positive regulation of oxidative stress and a negative regulation of antioxidant capacity [77]. Evidence indicates that antioxidant enzymes, including Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx), are altered in ASD patients, contributing to increased inflammation [78]. In summary, there is growing consensus in the scientific literature that immune dysfunction is a central component of the pathophysiology of ASD, reflecting a complex interplay of inflammatory mechanisms and oxidative stressors affecting neurological development. The KD exerts significant anti-inflammatory and antioxidant effects on the central nervous system through multiple metabolic pathways [79]. Jeong et al. demonstrated that KD reduces neuroinflammation via the activation of the peroxisome Proliferator-Activated Receptor Gamma (PPARγ), a transcription factor that regulates inflammatory responses and lipid metabolism homeostasis. Fatty acids, particularly medium-chain fatty acids present in the KD, activate PPARs, which are critical regulators of lipid metabolism and neuroinflammatory processes [80]. Additionally, Greco et al. revealed that ketone bodies, such as Beta-Hydroxybutyrate (BHB), exert beneficial effects on oxidative stress and mitochondrial function in a traumatic brain injury animal model [81]. Ketone bodies, produced during ketosis, serve as alternative energy substrates and modulate mitochondrial function by enhancing the activity of the mitochondrial respiratory complex and reducing Reactive Oxygen Species (ROS) production. KD likely normalizes mitochondrial function by stimulating mitochondrial biogenesis, which is mediated by the upregulation of the transcriptional coactivator PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1- alpha), thus decreasing oxidative stress and pro-apoptotic factors, preventing mitochondrial permeability transition, and reducing mitochondrial ROS levels in neocortical neurons.

Mirza, et al. [82] investigated the effects of propionic acid, a compound used to induce ASD- like behaviors in animal models, and found that propionic acid treatment led to increased oxidative stress and inflammation in the cerebellum, brainstem, and prefrontal cortex of the rats, with elevated levels of interleukin-6 (IL-6) and Tumor Necrosis Factor- Alpha (TNF-α) and decreased levels of interleukin-10 (IL-10) [82]. The KD was shown to mitigate these pathological changes, resulting in reduced oxidative stress and inflammation and improving the neurobehavioral disorders observed in these models. In summary, the KD offers neuroprotective effects through the modulation of metabolic pathways related to inflammation and oxidative stress [82]. By activating PPARγ, KD induces an anti-inflammatory response and protects against excitotoxic neuronal cell death [83]. Additionally, ketone bodies produced by the ketogenic diet promote mitochondrial biogenesis, enhance mitochondrial respiratory complex activity, and reduce ROS production, leading to overall improvements in neuronal health and a reduction in neurobehavioral symptoms associated with ASD.

Gut Microbiota

The gut microbiota is a complex and dynamic ecosystem comprising a diverse array of microorganisms, including bacteria, eukaryotes, and archaea, that inhabit the human gastrointestinal tract [84]. How is the intestinal microbiota formed? Vaginal delivery is the beginning of bacterial colonization of the body, with the genus Lactobacillus being the main intestinal bacterial flora of the newborn, as these bacteria are compatible with the mother's vagina. When birth occurs by cesarean section, the predominant bacteria are of the genus Clostridium. The Actinobacter and Proteobacter bacteria have their relevance in the first year of life, in the second year of life the Bifidobacterium and when they enter adult life, the Actinobacteria, Firmicutes and Bacteroidetes bacteria predominate. By adulthood the ratio of anaerobic/aerobic bacteria is 1000/1 [85]. The composition of intestinal microbiota has mainly four categories being Bacteroides, Firmicutes, Proteus and Actinomycetes and Proteus. As the proportion of Firmicutes/Bacteroidetes bacteria is a relevant parameter to reflect the disturbance of the intestinal microbiota [86]. The majority of these microorganisms colonize the colon, with an estimated bacterial population of approximately 3.8 x 10^13. A healthy gut microbiota is characterized by the predominance of two main bacterial phyla: Bacteroidetes and Firmicutes. In addition to these, other phyla such as Verrucomicrobia, Actinobacteria, and Proteobacteria are also present, albeit in significantly smaller proportions. The balanced and diverse composition of the gut microbiota plays a crucial role in maintaining human health, influencing processes such as digestion, immunity, and even behavior and mental health [87]. The primary genera within the gut microbiota include Alistipes, Faecalibacterium, Eubacterium, Bifidobacterium, Bacteroides, Dorea, and Ruminococcus [88]. Despite the consistent presence of these genera, there are significant variations in the proportions of these species among individuals. These differences can be influenced

by a multitude of factors, including diet, age, genetics, lifestyle, and environmental exposures. Such variability in the gut microbiota composition underscores the complexity and individuality of the human microbiome, which can have profound implications for personalized health and disease management. Understanding these variations is essential for developing targeted therapeutic strategies and optimizing interventions aimed at promoting a healthy microbiome. The colonization of the gut microbiota begins in the maternal womb and continues until around the age of three, at which point its composition and diversity resemble that of an adult [89]. Several factors influence the composition of the gut microbiota, including age, sex, and geographical location [90]. Additionally, stress, drug usage, dietary habits, and the presence of disorders and diseases also play significant roles [91]. These factors collectively shape the unique microbiota profile of each individual, impacting their overall health and susceptibility to various conditions. Understanding these influences is crucial for developing personalized therapeutic strategies aimed at maintaining or restoring a healthy gut microbiota.

Li, 2021 [92] demonstrated in a study that the Ketogenic Diet (KD) improved some behavioral symptoms in autistic individuals. They observed an improvement in scores obtained on the Autism Treatment Assessment Scale (ATEC) and the Childhood Autism Rating Scale (CARS), especially with regard to sociability. In another study, published by Lee and collaborators in 2018, it was observed that a modification of the KD, removing gluten consumption and supplementing it with Medium Chain Triglycerides (MCTs), was able to improve the subdomain scores of social affects and the total autism diagnostic observation schedule, 2nd edition (ADOS-2), although it did not affect restrictive and repetitive behavior on the scale. Through another dietary intervention, the authors observed that KD was responsible for improving social communication in one of six patients with Autism Spectrum Disorder (ASD); although this result was limited, the authors realized that KD was able to improve Attention Deficit Hyperactivity Disorder (ADHD) in all patients. Recent studies have shown that the gut interacts with the brain in a bidirectional manner, a phenomenon known as the gut-brain axis. What has drawn the attention of the scientific community is that the microbial communities residing in the gastrointestinal tract act as crucial regulators of this gut-brain connection. These communities, which form this biosocial environment, include bacteria, fungi, viruses, and other life forms collectively referred to as the microbiome [93].

On one hand, various physiological processes in the gut, such as gastrointestinal motility, secretion, and digestive functions, are modulated by the Central Nervous System (CNS) [94]. On the other hand, the intestinal microbiome influences brain function through neural, humoral, and immunological pathways [95,96]. More specifically, it is now widely accepted that this interaction occurs through three primary pathways: the immune pathway, the neuronal pathway, and the endocrine/systemic pathway, with interactions and cross-communications among these three [97]. The Central Nervous System (CNS) is susceptible to various dysfunctions during development, and altered immune conditions may contribute to pathological processes in Neurodevelopmental Disorders (NDDs) [98]. Specifically, the gut microbiota interacts with the immune system through its own presence, metabolites produced by microorganisms, such as Short- Chain Fatty Acids (SCFAs), secondary bile acids, and amino acid metabolites, as well as other bioactive molecules like Microbe-Associated Molecular Patterns (MAMPs) [99]. Together, these substances modulate local immunity within the gut, influencing the CNS via systemic circulation and playing a regulatory role with microglia as mediators. The gut microbiota serves as a crucial regulator of local enteric immunity. Bacteria, along with their metabolites, are essential for crossing the intestinal barrier and entering the bloodstream. Thus, the intestinal barrier plays a significant role in various physiological processes and in maintaining homeostasis within the CNS; [100]. For example, one of the most studied microbial metabolites, Short-Chain Fatty Acids (SCFAs), which are saturated fatty acids with fewer than six carbon atoms [101], help repair damage to the intestinal epithelium [102], and regulate tight junctions [103]. This strengthens the intestinal immune barriers, reducing intestinal permeability and preventing the entry of pathogenic agents [104]. Additionally, dysbiosis of the gut microbiota can modulate the integrity of the intestinal barrier, resulting in a "leaky gut" *(Fasano, 2020)* [105] and allowing the migration of pathogens into the portal and systemic circulation, which may contribute to neuroinflammation in central nervous system disorders, such as Autism Spectrum Disorder (ASD).

Gut Microbiota and Ketogenic Diet

The intestinal microbiota comprises a complex community of microorganisms that live in the digestive tract of animals, humans and even insects. In humans, the intestinal microbiota has one of the highest amounts of species of microorganisms in relation to other parts of the body [66]. The genes of intestinal microorganisms constitute a genetic repertoire that comprises an order of magnitude greater than the human genome [106]. Microorganisms, through their ability to modify many metabolic, neurochemical and immunological factors in the intestine, affect the nervous system and neurological functions [107]. From this perspective, much research has emerged correlating neuropsychiatric disorders and the microbial communities associated with ASD, Parkinson's disease, Alzheimer's disease, schizophrenia, depression, anxiety, and multiple sclerosis. Much research has been carried out using animal models that have limitations in synthesizing the complexities of human diseases. Although there is validation regarding the connections between neuropsychiatric disorders and the intestinal microbiota [108], new technological discoveries are being developed to validate mechanisms of biological action to offer real potential for the treatment of human diseases. There are discoveries

that support the role of the intestinal microbiota as a connection between the environment and genetic risk factors associated with ASD [109]. An increase in the Firmicutes/Bacteroidetes ratio was observed in patients with ASD, with this increase being associated with a reduction in Bacterioidetes [110]. A reduction in the genera Alistipes, Bilophila, Dialister, Parabacteroides and Veillonella was observed and an increase in Dorea, Collinsella, Corynebacterium and Lactobacillus, making reference to the strong association between the intestinal microbiota and the brain [111]. Communication with the brain and gut microbiota takes place through the gut-brain axis, in which the microbiota modulates brain development, metabolic homeostasis and immunity. When this communication is disrupted, it results in a variety of conditions including ASD [112]. There are findings that support the role of the gut microbiota as a link between the environment and genetic risk factors associated with autism spectrum disorder [113].

A pilot study conducted by *Allan, et al. (2024)* [114] suggests that the KD may in flu behavioral symptoms in children with ASD, in addition to the direct effect of ketones on brain metabolic activities. The KD was found to increase butyrate production, thereby enhancing gut microbial diversity. Once metabolized in the gut, the produced butyrate can enter the bloodstream and brain, directly promoting an anti-inflammatory state by acting on cytokines such as IL-1β or indirectly through interactions with neurotransmitters (e.g., acetylcholinesterase) [115] receptors like TLR2 [116], or miRNAs, such as those associated with BDNF [117]. The study suggested that the gut microbiome might affect the expression of epigenetic factors (e.g., miRNAs), which could indirectly influence brain activity through the gut-brain axis. This mechanism illustrates how the KD might impact ASD phenotypes, offering a potential avenue for therapeutic interventions. *Evangeliou, et al. (2003)* [118] conducted a clinical trial involving 30 children with ASD who followed a KD for six months. The results indicated that 7% of the participants showed significant improvement, while 53% exhibited mild to moderate improvement according to the Childhood Autism Rating Scale. Additionally, the study found that children with mild autism benefited the most from the ketogenic diet, highlighting its potential as a therapeutic. Human studies on the gut microbiome of individuals with ASD remain limited. However, animal model studies have shown promising results regarding the impact of the KD due to changes in the growth of microbial populations, which may, in turn, affect ASD symptoms. For instance, *Newell, et al. (2016)* [119] demonstrated an alteration in the Firmicutes/Bacteroidetes ratio in BTBR mice with ASD. Furthermore, the KD helped normalize the initially elevated population of Akkermansia muciniphila in these mice, a bacterium believed to have a positive association with ASD [120]. The study reported a reduction in the bacterial population by 78% in the cecum and 28% in the feces of BTBR mice following the KD. This suggests that the KD induced changes in the gut microbiome, highlighting its potential to correct the low Firmicutes/Bacteroidetes ratio and the common phenotype associated with ASD [119]. Additionally, *Ruskin, et al. (2013)* [121] found that BTBR mice fed a KD showed improvements in sociability, communication, and a reduction in self-directed repetitive behaviors. These findings underscore the potential of the KD in modulating gut microbiota and ameliorating ASD symptoms. Nevertheless, further human studies are necessary to substantiate the effects of the KD on the gut microbiota and its implicationsfor ASD treatment.tic intervention for improving ASD symptoms.

A review study carried out by *Liu, et al. (2019)* [122] presented important changes between the relationship between the intestinal microbiota in patients with ASD and typical patients, strengthening the evidence that intestinal microbiota dysbiosis is correlated with behavioral abnormalities found in ASD. *Xu, et al. (2019)* [123] proved in their review study that patients with ASD had a lower amount of Bacteroides, Bifidobacterium, E. coli, Akkermansia and Enterococcus, a greater abundance of Lactobacillus and Faecalibacterium and a slight increase in bacteria of the genera Clostridium and Ruminococcus. Significant differences were found in bacteria from the genera Bacteroides, E. coli, Bifidobacterium, Akkermansia and Lactobacillus when children with ASD were compared with typically developing children. In experimental models of ASD, such as those using rodent subjects, researchers have identified a significant overrepresentation of specific bacterial families including Porphyromonadaceae, Prevotellaceae, Bacteroidales, and Lachnospiraceae. These families were found to be more abundant in the gut microbiota of ASD models compared to control groups, indicating that the dysbiosis of gut microbiota might play a role in the manifestation and progression of ASD symptoms. Furthermore, an increasing body of research has demonstrated that disturbances in the gut microbiota are linked to various aspects of ASD, including its behavioral and cognitive symptoms. Interventions aimed at modulating the gut microbiota have shown promise in improving these symptoms. For example, recent studies suggest that therapeutic strategies targeting the gut microbiome, such as dietary modifications or probiotic supplementation, have the potential to alleviate some of the clinical manifestations of ASD and improve overall symptomatology in affected individuals. Individuals with ASD often exhibit distinct and atypical compositions of gut microbiota, along with unique metabolic byproducts resulting from their microbiome profiles. The gut microbiota communicates with the central nervous system through a complex network of signaling pathways involving the neuroendocrine, neuroimmune, and autonomic nervous systems, which together form the intricate and bidirectional communication axis known as the gut-microbiota-brain axis. This axis represents a critical pathway through which gut health influences brain function and, consequently, behavior and cognitive processes. A KD has demonstrated a notable capacity to restore the intestinal microbiota composition and improve key characteristics of ASD in animal

models. Research has shown that KD can effectively alter the gut microbiota, which is often dysregulated in ASD, leading to significant improvements in core ASD features such as social communication and repetitive behaviors. In experimental animal studies, KD was found to increase the abundance of beneficial gut bacteria such as Akkermansia, Parabacteroides, Bacteroides, and Desulfovibrio spp., which are known to play essential roles in maintaining gut homeostasis and modulating neuroinflammation. Despite the promising outcomes from animal studies, there is a significant gap in research concerning the effects of KD on gut microbiota and ASD symptoms in human populations. This highlights the necessity for further clinical investigations to explore the potential of KD as a therapeutic intervention for modulating gut microbiota in individuals with ASD. In summary, targeting the gut microbiota through KD interventions emerges as a novel and potentially effective therapeutic strategy for managing ASD symptoms, with future research required to elucidate the mechanisms underlying KD's effects and to evaluate its clinical efficacy in human trials.

Gut-Brain Axis in Autism

Studies are showing nervous, immunological and endocrine communication in the gut-brain axis that collaborate in the development of central nervous system diseases such as Alzheimer's disease, Parkinson's and ASD [124]. The way in which the central nervous system affects the intestinal microbiota is through the release of peptides associated with hunger, with intestinal motility regulated by cortisol through the hypothalamic-pituitary- adrenal axis, controlling the release of mucin produced by intestinal epithelial cells and intestinal motility through the neural pathways of the parasympathetic and sympathetic systems [125].

The intestinal microbiota constitutes a barrier of the mucosa, producing the integrity of the intestinal epithelium, highlighting the molecules that will pass into the blood. The occurrence of dysbiosis is the result of disruption of intestinal permeability facilitating the entry into the systemic circulation of metabolites, toxins and bacteria [126]. There is secretion and stimulation of pro-inflammatory cytokines such as IL-1, IL-6, IL-18 that are known to increase neuropsychiatric disorders and neuropsychiatric neurological disorders [127]. The epithelial cells of the intestinal microbiota, being compromised, allow the passage of bacteria such as Lactobacillus and products that are produced by the microbiota such as lipopolysaccharides, Gamma Aminobutyric Acid (GABA) and serotonin, thus resulting in the stimulation of the immune system present in the intestinal mucosa and, consequently, the release of inflammatory cytokines such as IL-6, IL-1 and TNF - α [128].

Brain functions are affected when dopamine, serotonin, GABA, short chain fatty acids, neuropeptides are secreted by enteric neurons directly affecting the vagus nerve or pass the blood- brain barrier. Corticotropin release via the cytokine-activated hypothalamic-pituitary-adrenocortical axis or the vagus nerve further enhances intestinal permeability by intestinal cytokine release [129]. Thus, the microbiota can affect the brain when it modifies the plasma levels of quinolinic acid, kynurenic acid and serotonin, in addition to the end products of tryptophan metabolism, which can cross the blood-brain barrier [130]. Immune abnormalities have been reported in children with ASD such as increased production of cytokines necessary for neurodevelopment, especially children with the regressive subtype of the disorder [131]. In addition, there is an increase in plasma pro- inflammatory cytokines such as IL-1B, IL-6, IL-8 and IL-12 platelet-derived growth factor and macrophage migration inhibitory factor [132] Changes in beta growth factor, p-selectin and macrophage migration inhibition factor have been associated with communication deficits, hyperactivity and stereotypical communication [133].

Postmortem brain samples from individuals with ASD showed significant discoveries about neuroinflammation [134]. A study that analyzed autopsy samples of cerebrospinal fluid from individuals with ASD, demonstrated neuroinflammatory responses involving increased profiles of pro-inflammatory cytokines and activation of microglia [135]. Microglia are phagocytic cells that, in addition to immunological surveillance, play an important role in the development and synaptogenesis of the central nervous system [136]. In mouse models neurodevelopmental disorders and microglial deficits were associated with low synaptic transmission, reducing brain functional connectivity, increased repetitive behavior phenotypes and deficits in social interactions [137].

Recent studies have revealed the importance of the intestinal microbiota in the context of neurodevelopmental disorders [70]. The link known as the gut microbiome- brain axis has been the subject of several investigations on global scale, with the aim of improving behavioral symptoms in individuals with autism [138]. Evidently, the gut microbiota plays a role in triggering inflammatory processes through the release of pro- inflammatory metabolites and mediators, which enter the Central Nervous System (CNS) via the bloodstream and cause neuroinflammatory events [139,140].

Microbiota Treatments

Probiotics were first described by Elie Metchnikoff, a Nobel Prize winner in the early 20th century. Since then, the field of probiotic research has expanded significantly, with a variety of studies highlighting their extensive and noteworthy health benefits [141]. The promising results of probiotic interventions have generally been validated in preclinical models. The potential therapeutic roles of probiotics have been explored across various medical domains, including psychiatry, gastroenterology, cardiology, dermatology, neurology, gynecology, and oncology [141] The use of probiotics as a promising therapeutic approach in psychiatry has gradually evolved since the early 2000s. Understanding the bidirectional interaction between the human brain and gut microbiota within

the Microbiota-Gut-Brain Axis (MGBA) has opened new avenues for exploring the potentially beneficial role of probiotics in the complex and still underexplored field of mental health. Given the relatively high prevalence of Gastrointestinal (GI) disorders in individuals with ASD and the Gut-Brain Axis (GBA) theory, many studies have examined the therapeutic effects of probiotics on ASD [142]. The GBA is a crucial pathway for communication between the gastrointestinal system and the central nervous system in mammals. This axis consists of sympathetic and parasympathetic branches of the central nervous system, neuroendocrine system, autonomic nervous system, enteric nervous system, intestine, and intestinal microorganisms along with their metabolites [143]. Intestinal microorganisms transmit information through the enteric nervous system to the vagus nerve, which then reaches the central nervous system, influencing psychological, cognitive, behavioral, and neurological functions. Probiotics are living microorganisms that, when administered in adequate amounts, provide health benefits to the host [144]. They produce and transport neuroactive substances and act within the gut-brain axis, such as Gamma-Aminobutyric Acid (GABA) generated by Lactobacillus brevis and Bifidobacterium denticola, and dopamine produced by Staphylococcus aureus and Escherichia coli [145]. For this reason, Dinan et al. classified them as psych biotics. Numerous probiotic species have been utilized to address Autism Spectrum Disorder (ASD), including single-strain probiotics, mixtures of different formulas, and probiotic products, often combined with dietary or behavioral interventions. Lactobacillus reuteri and Lactobacillus plantarum have shown significant improvements in social behavior in mice; however, there is insufficient evidence to confirm that probiotics have positive therapeutic effects on ASD in children [146].

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host. This definition has been established and is widely accepted by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO). Probiotics are predominantly bacteria, but they can also include yeasts and other types of microorganisms. They are naturally found in a variety of fermented foods, such as yogurt, kefir, sauerkraut, kimchi, and other fermented dairy products. Additionally, probiotics are available in the market as dietary supplements, often in the form of capsules, powders, or beverages, allowing consumers to easily integrate them into their daily routines. Probiotics exert their beneficial effects through various mechanisms that work synergistically to promote intestinal and overall health. They are resistant to the gastrointestinal environment (pancreatic and bile secretions) [147]. The most used probiotic species are yeasts such as Saccharomyces boulardii, Lactobacillus, Bifidobacteria [148]. One of the primary mechanisms is competitive exclusion, where probiotics compete with pathogenic microorganisms for adhesion sites on the epithelial cells of the intestine. This reduces the colonization of pathogens, helping to prevent infections and gastrointestinal disorders. Another important mechanism is the improvement of the mucosal barrier. Probiotics help strengthen the integrity of the intestinal barrier, which is crucial for gastrointestinal health, as a compromised intestinal barrier can lead to conditions such as leaky gut syndrome, which is associated with various inflammatory and autoimmune diseases. The integrity of the intestinal mucosa is fundamental, as it acts as a first line of defense against pathogens and toxins. Furthermore, probiotics play a significant role in immune modulation. They can influence the host's immune response, promoting a healthy balance between Th1 and Th2 responses. This balance is important for the prevention of allergic and autoimmune diseases, as an unregulated immune response can result in hypersensitivity to allergens or attacks by the immune system on the body's own cells. Probiotics are also known for their ability to produce beneficial metabolites, such as short-chain fatty acids, which have anti- inflammatory effects and promote intestinal health by contributing to the nutrition of colon cells and helping to regulate metabolism.

In terms of immune health, regular consumption of probiotics can enhance the immune response, reducing the incidence of respiratory and gastrointestinal infections. This is particularly relevant in vulnerable populations, such as children and the elderly, who may significantly benefit from the immune support provided by probiotics. Moreover, there is emerging evidence suggesting that probiotics may influence mental health. This influence may occur through the communication between the gut and the brain, a phenomenon known as the gut-brain axis. This connection suggests that gut health can have a direct impact on emotional and psychological well-being, leading to a growing interest in the use of probiotics as a complementary approach in the treatment of mood disorders, such as anxiety and depression. Another interesting aspect is the relationship between probiotics and weight control. Studies indicate that certain probiotics may help regulate body weight and reduce visceral fat, a type of fat associated with a higher risk of metabolic diseases, such as type 2 diabetes and cardiovascular diseases. While more research is needed to confirm these effects and understand the underlying mechanisms, these findings are promising for the development of weight control strategies based on dietary interventions. Research in this field is continually evolving, and new studies are being conducted to explore how different strains of probiotics may affect metabolism and body composition. Recent studies suggest that probiotics may play an important role in the treatment of children with ASD, particularly concerning the gastrointestinal and behavioral symptoms associated with the condition. Children with ASD often exhibit alterations in the composition of their gut microbiota, a phenomenon known as dysbiosis. Some studies indicate an increase in the abundance of bacteria such as Bacteroides, Parabacteroides, Clostridium, Faecalibacterium, and Phascolarctobacterium, while others, like Coprococcus and Bifidobacterium, are found in lower

quantities compared to neurotypical children. This dysbiosis can lead to intestinal inflammation, increased intestinal permeability, and the production of potentially neurotoxic metabolites, such as short-chain fatty acids. These factors may contribute to the common gastrointestinal symptoms seen in ASD, as well as influence brain development and function.

Probiotics have shown promise in addressing some of these issues. Studies in animal models suggest that supplementation with probiotics, particularly strains like Lactobacillus reuteri, can improve certain autism-like behaviors. Possible mechanisms for these effects include the restoration of gut microbiota balance, reduction of intestinal inflammation, improvement of intestinal barrier integrity, modulation of immune response, and increased production of beneficial neurotransmitters, such as oxytocin. For instance, a study in mice demonstrated that supplementation with L. reuteri restored levels of this probiotic and improved socialization and brain plasticity. While the results are promising, it is important to note that more research is needed to confirm the effects of probiotics in children with ASD. Several critical points should be considered: not all probiotic products possess the same quality and efficacy, and regulation in this area is limited, meaning that composition can vary significantly. Additionally, different strains of probiotics may have distinct effects, and indiscriminate use could lead to bacterial resistance (Figure 1).

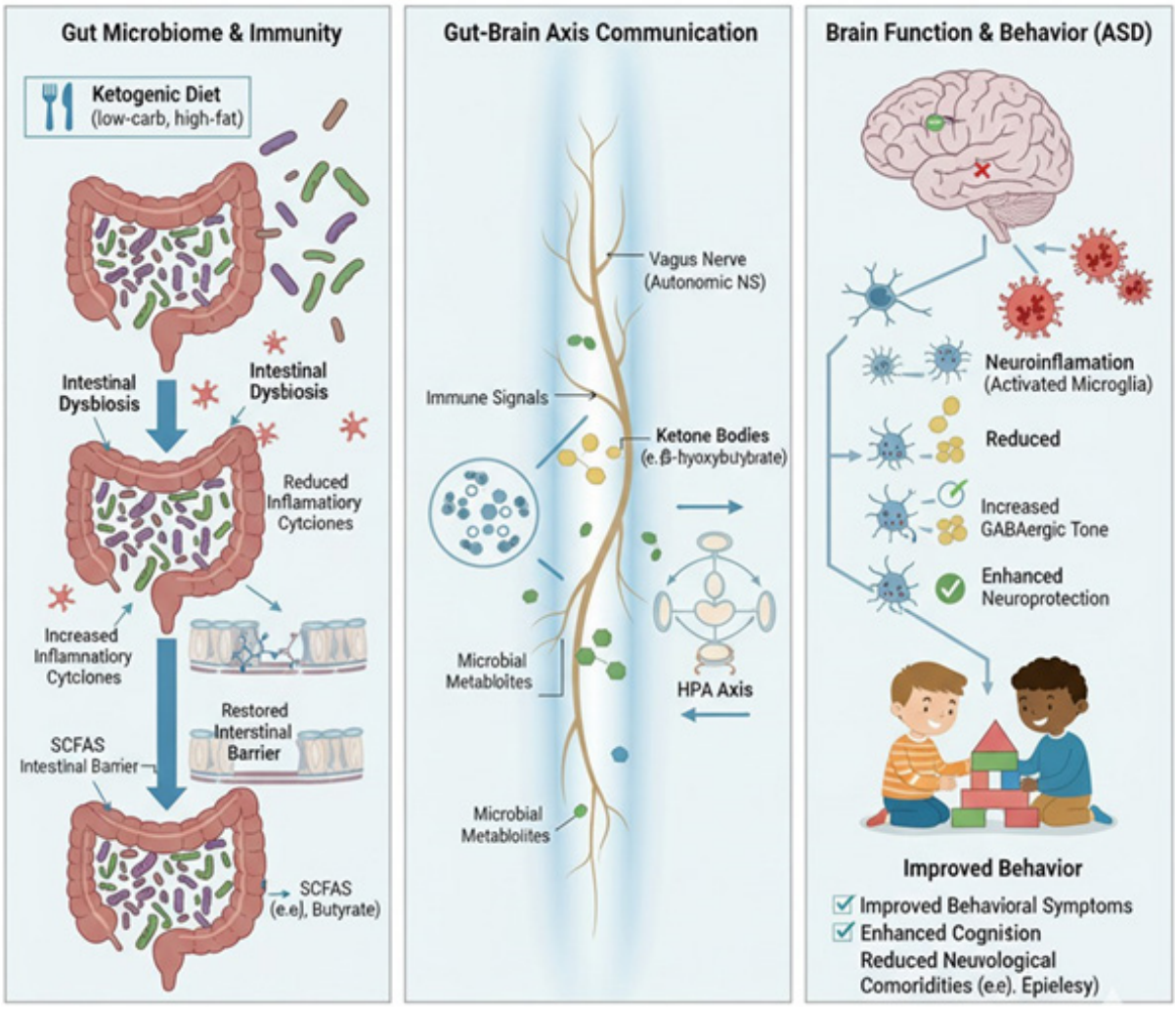

Figure 1: Dietary changes may contribute to the worsening of ASD and other neurological disorders.

The correlation between Gastrointestinal Tract (GIT) inflammation, microbiota dysbiosis, and the neurological symptoms of ASD is mediated by the complex Gut-Microbiota-Brain Axis. The Ketogenic Diet (KD), characterized by severe carbohydrate restriction, represents a dietary intervention with therapeutic potential in this context, acting through multiple mechanisms. At the GIT level, the KD, by drastically altering the dietary substrate, reshapes the composition of the gut microbiota, affecting the

profile of microbial metabolites (such as Short-Chain Fatty Acids - SCFAs) and modulating intestinal inflammation, which is frequently correlated with symptom severity in ASD. At the Central Nervous System (CNS) level, the state of ketosis induced by the diet leads to the production of ketone bodies (e.g., β-hydroxybutyrate), which not only provide an alternative energy source for the brain but also exhibit neuroprotective effects and modulate neural activity, including the regulation of inhibitory neurotransmitters, such as GABA. Thus, the KD integrates the communication pathways of the axis (including the immune system and neuronal routes) to potentially reduce neuroinflammation and cerebral excitability, resulting in observed improvements in core behavioral symptoms and neurological comorbidities associated with ASD.

Conclusion

ASD is a multifaceted neurodevelopmental disorder characterized by a broad spectrum of symptoms affecting social interaction, communication, and repetitive behaviors. Effective and timely intervention is essential for improving the long-term prognosis of individuals with ASD, yet there remains no universally effective treatment that can fully address all the core symptoms associated with the disorder. Among the therapeutic strategies explored, the Ketogenic Diet (KD) has emerged as a potentially effective intervention for ameliorating certain behavioral symptoms of ASD. This diet has demonstrated the capacity to positively influence ASD-related behaviors through several mechanisms, including the normalization of GABAergic neurotransmission, enhancement of mitochondrial function, reduction of neuroinflammation and oxidative stress, inhibition of the mTOR signaling pathway, and modulation of gut microbiota composition. However, the therapeutic efficacy of KD exhibits significant variability among individuals with ASD, and the exact mechanisms underlying its effects are not yet fully elucidated. Additionally, the practical application of a KD in pediatric ASD populations is complicated by selective eating behaviors, which can pose challenges to the successful implementation of this dietary approach. Consequently, while KD holds promise as a therapeutic strategy for improving ASD symptoms, further research is necessary to better understand its mechanisms of action and to address the practical obstacles associated with its clinical application.

Our hypothesis is based on the high increase in cases of ASD diagnosis around the world, which drew our attention to several factors. Firstly, the subjectivity of diagnostic tests and the possibility of false positive results are relevant aspects to consider. Secondly, the possible cause of the increase in ASD cases throughout human evolution is also a point of interest. This second theory can be considered, since we demonstrated in this article that the nutritional factor is intrinsically related to several metabolic disorders, such as hypertension, obesity, diabetes and neuropathology. Although we recognize the lack of conclusive data for a definitive diagnosis of ASD, we also have evidence that intestinal cells are directly linked to the brain. Changes in the homeostasis of the intestinal microbiome can cause significant changes in the central nervous system, increasing neuroinflammation and causing neuropathologies. Based on our study, we believe that the previously mentioned approaches to improving the condition of patients with ASD can be significantly beneficial. Not just an isolated approach, but a combination of them can be more effective. This includes replacing the consumption of A1 milk with A2 milk, associated with a low carb or ketogenic diet. These measures can help modulate the gut microbiome, reduce neuroinflammation, and improve ASD symptoms.

Materials and Methods

We utilized electronic databases including PubMed (MEDLINE), Scopus, and Google Scholar for our research. The combined search terms included "low-carbohydrate diet," "very low-calorie diet," "ketogenic diet," "autism," "gut-brain axis," "autism spectrum disorder," "ASD," "ASD and diet," "ASD and ketogenic diet," "ASD and gut microbiota," and "microbiota." All topics related to these terms were explored, with a priority given to articles published from 2020 onward. Eligibility criteria included full- text articles, clinical cases, and reviews written in English and Portuguese (Brazil). The references of the retrieved articles were also tracked. Abstracts, case reports, and editorials were not retained for this analysis.

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Conflict of Interest

None.

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