Int J Nutr Sci 2025;10(4):2-16

International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Conventional versus Modified Ketogenic Diets in Autism Spectrum Disorder: Transforming and Shaping Future Approaches

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ARTICLE INFO

Keywords:
Autism spectrum disorder
Ketogenic diet
Modified ketogenic diet
Cognitive behaviour
Gut health

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Received: July 19, 2025
Revised: October 8, 2025
Accepted: October 18, 2025

ABSTRACT

Recently researchers have highlighted the advantages and disadvantages of modified ketogenic diet (MKD) and optimum use of this dietary intervention for providing personalised nutrition in individuals having Autism Spectrum Disorder (ASD). This study aimed to provide a comprehensive review and analysis of the effects of the Ketogenic Diet (KD) and its MKD on individuals with ASD. The KD is a high-fat, low-carbohydrate dietary regimen that mimics the metabolic state of fasting by triggering ketosis, a process where the body shifts from using carbohydrates to fats as its primary energy source. The MKD, a more flexible adaptation of the traditional KD, permits a slightly higher intake of protein and carbohydrates; while still sustaining ketosis. Both diets have shown potential in influencing key factors associated with ASD, including neurotransmitter activity, gut microbiome composition, cognitive function, behavior, and overall quality of life. This review delves into the mechanisms by which KD and MKD may benefit individuals with ASD, drawing insights from both animal models and human case studies. Additionally, it explores the therapeutic potential and limitations of these dietary strategies, particularly in addressing co-occurring conditions frequently observed in those with ASD. Through this analysis, the study seeks to shed light on the promise of nutritional interventions (carbohydrate modification, addition of probiotics, omega 3 fatty acids and selenium) in the broader management of autism-related challenges.

Please cite this article as: Dutta P, Vats M, Pal S, Chakraborty S. Conventional versus Modified Ketogenic Diets in Autism Spectrum Disorder: Transforming and Shaping Future Approaches. Int J Nutr Sci. 2025;10(4): doi:

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition where the affected individuals exhibit a range of symptoms such as difficulties in social interaction, communication challenges and repetitive behaviours, sensory sensitivities and cognitive challenges (1, 2). There are several types of diets which are found to be immensely beneficial in reducing the aforementioned symptoms of ASD (3). In 1925, improvements in patients' behaviour and cognitive functioning on the ketogenic diet (KD) together with decreased irritability, increased alertness, better sleep, and improved discipline among

children were demonstrated. KD was shown as a high-fat, low-carbohydrate diet that shifted the body's metabolism from glucose to ketone bodies (4, 5). This is typically characterised by a significant reduction in carbohydrate intake (<20-50 g/day), alongside a considerable increase in fat consumption contributing to 70-80% of the total calorie intake (6).

Protein is typically maintained at 10–20% of daily energy needs, as excess amounts may convert to glucose via gluconeogenesis, disrupting the ketosis essential for KD's therapeutic effects (6). This metabolic shift has been shown to influence the brain function and neurotransmitter balance, making it a promising approach for managing neurological conditions in patients suffering from ASD (6-9). These neuroprotective effects along with metabolic effects of KD, such as reducing oxidative stress and improving mitochondrial function indicate that KD can possibly help to address the key symptoms of ASD (10). Positive effect of KD has been established in stabilising neuronal activity, thereby contributing to improvements in behaviour, social interactions and overall cognitive function in ASD affected individuals (11, 12).

Present knowledge indicates that KD has few limitations and challenges which can be overcomed by the use of modified KD (MKD) i.e., combining one or more diet with traditional KD (13). MKD offers more flexibility with slightly higher carbs and fat than KD, while still preserving ketosis. This makes it more sustainable long-term, especially for managing epilepsy and ASD (14). Recently researchers have highlighted the advantages and disadvantages of MKD and optimum use of this dietary intervention for providing personalised nutrition in individuals having ASD (15, 16). This review delved into recent studies and case reports on the effects of KD and MKD on ASD-related physiology in both animal models and humans and outlined the key benefits and drawbacks of each diet (17).

Materials and Methods

In this review, we have used a well-organized search strategy system (Figure 1) such as SciVerse Scopus® (Elsevier Properties S.A, USA), Web of Science® (Thomson Reuters, USA), and PubMed® (U.S. National Library of Medicine, USA). Common searching keywords or phrases used were 'ASD', 'Ketogenic diet', 'ASD treatment', 'Neuro developmental disorder', and other related ones. A total of 202 non-duplicate English articles have been identified in the initial phase and 116 relevant articles have been selected after initial screening. Finally, 99 most relevant articles were selected while the remaining 17 were excluded.

Composition and Types of Conventional KD

Composition and types of conventional KD have been described in Table 1 and varieties of KD and their macronutrient contents in Figure 2 and Figure 3.

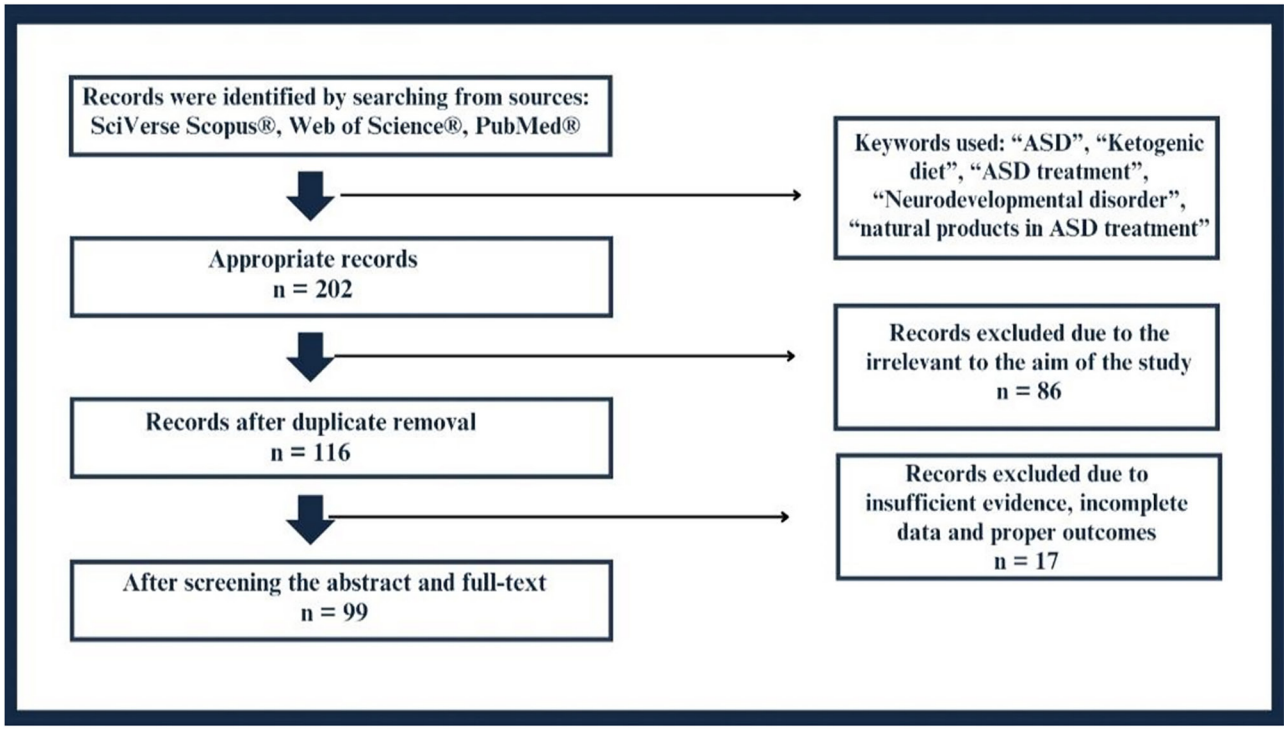

Figure 1: Flow diagram of literature search and selection.

Table 1: Composition of conventional KD.

Type of diet for ASD	Composition of diet	Details of the diet and mode of action	Reference
KD	70% fats, 20% protein and 10% carbohydrates and is beneficial for alleviating core symptoms	Improves the balance between inhibitory GABA and excitatory glutamate, enhancing neural regulation. This helps reduce excessive excitation and improves cognitive and behavioral outcomes in ASD	(16)
Targeted KD	Targeted KD allows extra carbohydrates during intense workouts without disrupting ketosis benefits like enhanced mitochondrial function and reduced oxidative stress in individuals with ASD	This variation is designed to allow intermittent relief from the strictness of continuous ketosis while still reaping the benefits of KD	(17)
HPKD	High protein (35%) along with 60% fat and 5% carbohydrates	HPKD supports ketosis, growth, and muscle development, especially in children and adolescents. Higher protein intake also stabilizes blood sugar and boosts cognitive function	(18)
CKD	CKD involves periodical intake of higher-carbohydrate diet in between KD cycles, such as five days of KD followed by two days of higher-carbohydrate diet in a cycle	Research shows CKD helps maintain cognitive function and energy, benefiting individuals with ASD, especially those with energy dips on continuous KD	(17)

ASD: Autism spectrum disorder, CKD: Cyclical ketogenic diet, GABA: Gamma aminobutyric acid, HPKD: High-protein ketogenic diet, KD: Ketogenic diet, MKD: Modified ketogenic diet.

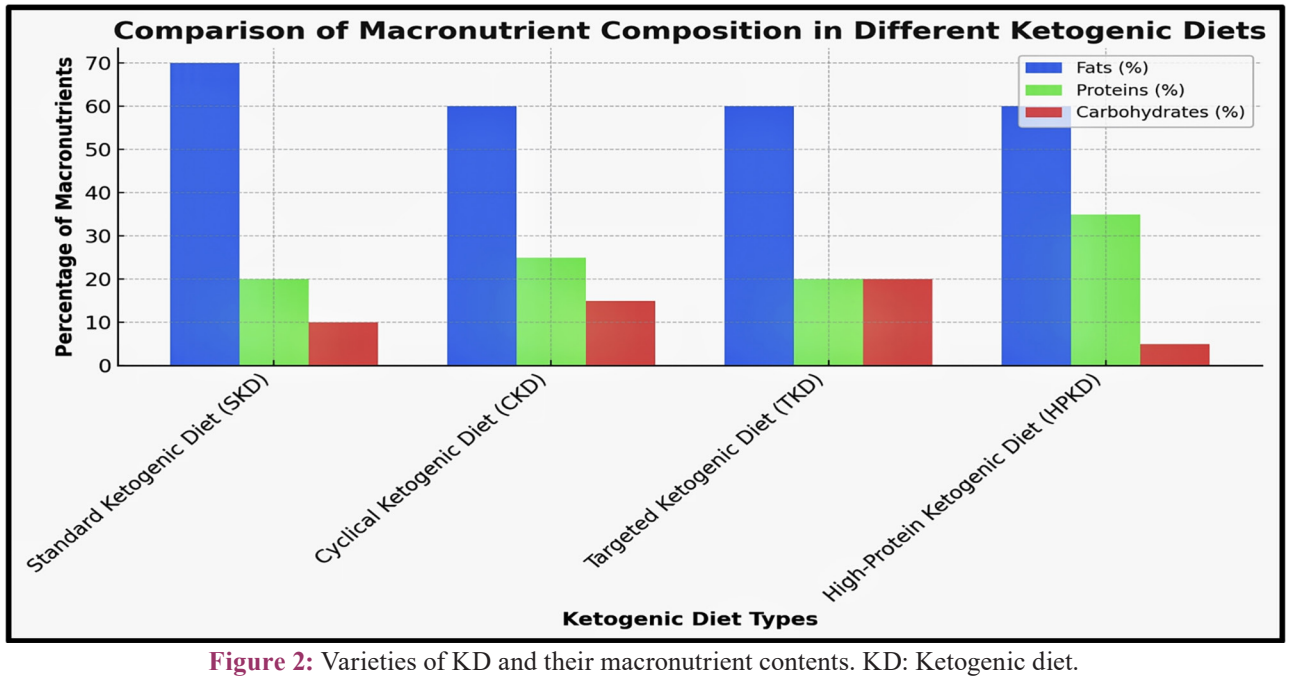

Figure 2: Varieties of KD and their macronutrient contents. KD: Ketogenic diet.

Modified Ketogenic Diet

(a) KD Modified with Medium-Chain Triglyceride (MCT)

The MCT diet has been utilized since the 1970s incorporating a higher proportion of highly ketogenic oil in the diet to allow a greater carbohydrate intake. Few researchers conducted a study to evaluate the efficacy of the MCT diet on children with epilepsy (18-20). Their findings showed that although the classic KD led to higher ketone levels, it also caused more fatigue and mineral deficiencies. However, both diets showed no major differences in growth, efficacy, or overall tolerability (21, 22).

(b) KD Combined with Atkins Diet

MAD starts without fasting or calorie restrictions limits carbs to 10 g/day for children and 20 g/day for adults, with high fat to sustain ketosis. In a study of 280 patients, 44% reported ~50% seizure reduction, and 26% had over 90%, highlighting MAD's effectiveness (22). Children who could gradually move from MAD to a full-fledged KD and had myoclonic-astatic epilepsy along with ASD have also experienced prominent health benefits (23).

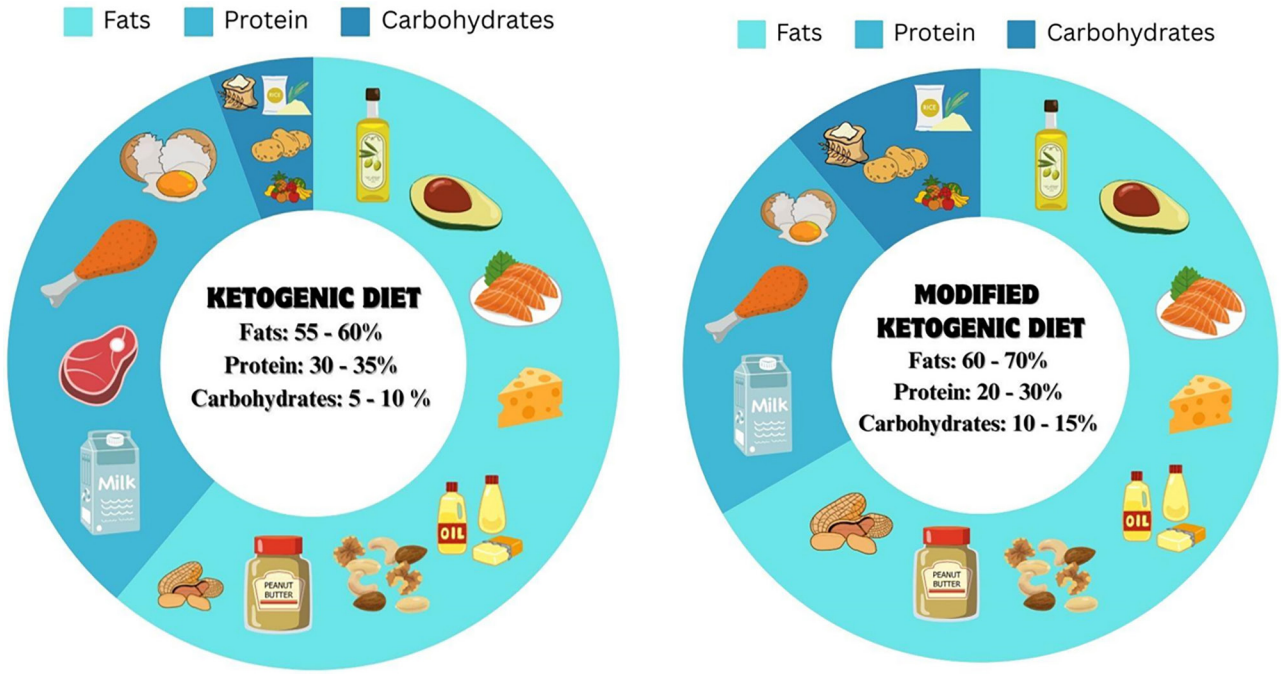

Figure 3: Composition of KD and MKD. KD: Ketogenic diet, MKD: Modified ketogenic diet.

(c) Low Glycemic Index Treatment (LGIT)

LGIT was first published with the goal of providing carbohydrates with glycemic indices <50 in order to maintain stable blood glucose levels in ASD patients. Although serum ketones increase, they are considered minimal and it is started as an outpatient without a fast (24). Later it has revealed that 50% of the children staying on LGIT diet for 3 months had >50% reduction in occurrence of seizure (24).

(d) Modified Ketogenic Gluten-Free Diet with MCT

A modified ketogenic gluten-free diet regimen with supplemental MCT was implemented in 15 children (aged between 2 to 17 years) for 3 months. Clinical (Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), Childhood Autism Rating Scale, Second Edition (CARS-2)) and biochemical parameters were investigated at the baseline and post 3-months of having the MKD (25). MKD limits net carbs to 20-25 g/day, allows protein up to twice the RDA, and meets remaining energy needs with various fats. The study also recommends MCT sources like coconut or pure MCT oil for 20% of energy, and suggests gluten restriction (26, 27).

Implications of KD and MKD on Various Physiological Functions of ASD Patients

Both these KD and MKD have significant effects on the neurotransmitter levels, brain function, immunity, inflammation etc. (25) (Figure 4).

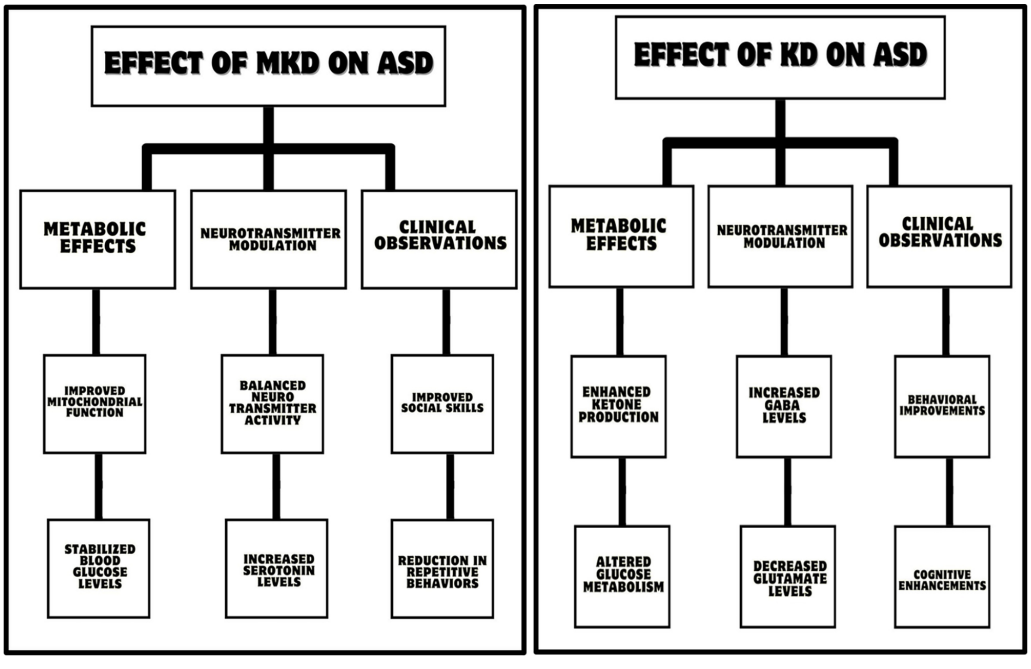

Figure 4: (A) Effect of KD on ASD, (B) Effect of MKD on ASD. ASD: Autism spectrum disorder, KD: Ketogenic diet, MKD: Modified ketogenic diet.

Table 2: Effect of KD and MKD on the neurotransmitter levels of the ASD patients.

Neurotransmitter	Function	Disruption in ASD	Effect of KD	Effect of MKD	Reference
GABA	Primary inhibitory neurotransmitter that calms neuronal activity, reduces anxiety, promotes relaxation and maintains balanced neural communication	Individuals with ASD often have a deficiency of GABA, leading to heightened anxiety, irritability and difficulty in social interactions	Increases GABA levels, promoting a balance between inhibitory and excitatory neurotransmitters, which helps to reduce anxiety and improve social interactions	Similar to KD, MKD may also increase GABA levels at a little slower pace, offering long-term benefits in balancing excitatory and inhibitory neurotransmission	(26, 27)
Glutamate	Main excitatory neurotransmitter involved in cognitive functions such as learning ability and memorizing power, Excessive activity can lead to excitotoxicity and neuronal damage	Excessive glutamate activity is often observed in ASD, contributing to neural overexcitation and potential neuronal damage	Reduces excessive glutamate activity, promoting a balanced state between inhibitory and excitatory neurotransmitters	MKD may help reduce excessive glutamate levels and prevent excitotoxicity, promoting cognitive function improvements	(24, 26)
Serotonin	Regulates mood, social behavior, appetite, sleep, memory and sexual function. Low levels are associated with depression, anxiety and sleep disorders	Altered serotonin levels and metabolism in ASD contribute to mood disturbances and social interaction difficulties	Enhances serotonin synthesis and availability by improving mitochondrial function and reducing inflammation	MKD enhances serotonin synthesis, reducing inflammation and improving mood disorders associated with ASD	(26, 33)
Dopamine	Crucial for reward, motivation, attention and motor control; Dysregulation is linked to ADHD, Parkinson's disease and mood disorders	Dopamine dysregulation can contribute to repetitive behaviours and challenges with motivation and attention in ASD	Modulates dopamine levels, potentially improving attention, reducing repetitive behaviours and enhancing motivation	MKD regulates dopamine but with less pronounced effects than KD, improving attention and motivation	(28-29)
Norepinephrine (Noradrenaline)	Involved in attention, arousal and the fight-or-flight response; Helps maintain alertness and focus and regulates mood	Imbalances are associated with anxiety and attention disorders	Influences norepinephrine levels, potentially improving attention and reducing anxiety	MKD may also positively influence norepinephrine stabilizing the stress response and enhancing cognitive functions	(30, 35)
Epinephrine (Adrenaline)	Primarily involved in the body's stress response, increasing heart rate and energy availability; Plays a role in cognitive function and emotional regulation	Altered stress responses and cognitive function can be linked to epinephrine levels	Overall improvements in neurotransmitter balance and reduced stress responses may indirectly benefit individuals with ASD	MKD may also help regulate epinephrine levels, contributing to the stabilisation of the stress response and cognitive function; the effect might be somewhat less pronounced compared to the classical KD	(33, 36)

ASD: Autism spectrum disorder, GABA: Gamma aminobutyric acid, KD: Ketogenic diet, MKD: Modified ketogenic diet.

Role of Neurotransmitters and Brain Function

KD shifts energy use from glucose to ketones, offering a more stable brain energy supply. This enhances metabolism, supports neuronal function, synaptic plasticity, and stabilizes brain activity in individuals with ASD (26). An improvement in the reduction of seizure attacks and involuntary movements in patients (>50%) diagnosed with both ASD and epilepsy and who underwent KD at least for one month was demonstrated (27). A significant reduction in fear, anxiety, and emotional disturbances was also reported by Various *et al*., 2021 and explored an anti-seizure mechanism of KD, which was the increase of GABA in the brain (18). Neurotransmitters play a critical role in regulating brain functions such as mood, cognition, behaviour and overall neuronal communication that were elaborated in Table 2.

Effect of KD and MKD on the Neurotransmitter Levels of the ASD Patients

Key neurotransmitters include GABA, glutamate, serotonin, dopamine, norepinephrine and epinephrine. The balance and function of these neurotransmitters are vital for normal brain functioning and are often disrupted in neurological conditions such as ASD (28-32). By modulating levels of GABA, glutamate, serotonin, dopamine, norepinephrine and epinephrine, both KD and MKD can potentially improve mood, behaviour and

Table 3: Effect of KD and MKD on immunity and inflammation.

Immunity and inflammation indicators	Alterations due to ASD	Effects of KD	Effects of MKD	Reference
Regulatory T Cells (Treg)	Crucial for maintaining immune tolerance and preventing autoimmune responses, which may be specifically relevant for ASD affected individuals with immune dysregulation	It enhances Treg function and number, crucial for maintaining immune tolerance and preventing autoimmune responses in ASD	With potential modulation of Treg activity to support immune regulation in ASD	(39-41)
Effector T cells	KD has the potential to modulate the immune system by influencing the balance between pro-inflammatory and anti-inflammatory effector T cells; This shift towards a more anti-inflammatory profile may be beneficial in managing the inflammation associated with ASD, offering a promising therapeutic approach for alleviating related symptoms	Promotes a shift towards a more anti-inflammatory profile of effector T cells, beneficial for managing ASD-related inflammation	May further refine the balance of pro-inflammatory and anti-inflammatory T cells, enhancing immune response in ASD	(41, 42)
B cells	In ASD, B cells may produce elevated autoantibodies, contributing to immune dysfunction	Influences B cell function, potentially reducing autoantibody levels often elevated in autoimmune conditions associated with ASD	Likely supports similar benefits in B cell modulation, reducing the risk of autoimmune reactions in ASD	(43, 44, 46)
Macrophages	In ASD, macrophages may skew toward a pro-inflammatory state, increasing cytokine production and contributing to chronic inflammation	Promotes polarization towards an anti-inflammatory phenotype (M2), reducing pro-inflammatory cytokine production and supporting tissue repair	May enhance the anti-inflammatory effects of macrophages, further aiding in managing inflammation in ASD	(47, 49, 50)
Microglia	Microglia, the brain's immune cells, are abnormally activated in ASD, leading to chronic neuroinflammation and disrupted neural function	Modulates microglial activation, promoting an anti-inflammatory state and reducing neuroinflammation relevant to ASD	Similar modulation of microglial activity, potentially amplifying the anti-inflammatory effects in the brain	(50, 51)

ASD: Autism spectrum disorder, GABA: Gamma aminobutyric acid, KD: Ketogenic diet, MKD: Modified ketogenic diet.

cognitive function in individuals with ASD (33-35). Besides its effects on epilepsy, KD offers many additional benefits, including improved energy, memory, social functioning, quality of life (QOL) and reduced negative affect (36-38). Both diets are rich in antioxidants with anti-inflammatory properties that improve cognitive and social functions and reduce anxiety and memory issues (39-41). However, further research is still needed to fully understand their long-term benefits in managing ASD (42-45) (Figure 4).

Immunity and Inflammation

In individuals with ASD, immune dysregulation and chronic inflammation are often observed, potentially contributing to the disorder (46-48). KD, known for its anti-inflammatory and neuroprotective effects, has shown potency in modulating immune responses and reducing inflammation in ASD (49, 50). Many with ASD have altered immunoglobulins, increased autoantibodies, and elevated cytokines, contributing to neuroinflammation (51-53). Intervention of KD has been found to mitigate these symptoms as illustrated in Table 3.

Effect of KD and MKD on Immunity and Inflammation

Research has found that autoantibodies against brain epitopes in mothers of children with ASD and in many ASD-affected children are strongly correlated with allergic symptoms, suggesting an aberrant immune response and disruption of the blood-brain barrier (BBB) (54-59). KD has been shown to reduce levels of key pro-inflammatory cytokines such as Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α), (60, 61). KD may work by targeting 'out of control' immune activation in Drug-Resistant Epilepsy (DRE) and in refractory status epilepticus (SE) (62, 63). Further research is needed to optimize KD as a therapy, as immune dysregulation and inflammation are key in ASD diagnosis and treatment (64).

Gut Health and Microbiota

Recent studies suggest that KD may remodel gut microbiome composition which in turn can possibly provide protective effects on various central nervous system (CNS) disorders (65). In a separate study carried out on 14 epileptic infants and 30 healthy infants, it was observed that after one week of receiving KD therapy, 64% of the epileptic infants experienced a significant reduction in occurrence of seizures (66). Dysbiosis, or an imbalance in the gut microbiome, is commonly observed in individuals with ASD. KD can significantly alter the composition of these gut microbiomes, leading to potential health benefits (67-69). KD and its modified versions reduce Prevotella levels and promote beneficial bacteria, restoring gut balance and alleviating many ASD symptoms (70). KD has been shown to promote the growth of beneficial bacteria such as *Akkermansia*, *Bifidobacterium* and *Lactobacillus* as well and reduces the abundance of pathogenic bacteria, such as *Clostridium* and *Escherichia coli*, which are linked to gut inflammation and dysbiosis, common conditions of ASD (71, 72).

The gut barrier prevents harmful substances from entering the bloodstream and allows nutrient absorption. Impaired function or "leaky gut" is common in individuals with ASD (73). Li *et al.* (2021) demonstrated that KD could restore gut barrier function by reducing gut permeability and inflammation in a rodent model of neurodevelopmental disorders (l Limited research links KD to the gut microbiome in autism, but animal studies showed promising results. In mice, it was shown that KD could alter the gut bacteria, improve gut health, and reduce gastrointestinal issues, with a 78% drop in cecal and 28% in fecal bacterial abundance (72). KD therapy enhances tight junctions, reduces intestinal permeability and prevents harmful substances from entering the bloodstream, and alleviates autism symptoms. Together, these findings suggest that KD may play a role in managing gastrointestinal and neurobehavioral symptoms in autism (73, 74).

Emerging research highlights a strong correlation between gut health and behavioural symptoms in individuals with ASD (75, 76). The gut-brain axis influences behavior, mood, and cognitive functions like focus and learning, suggesting that improving gut health can reduce hyperactivity, irritability, and repetitive behaviors (77-79). These changes are thought to be mediated by the production of neurotransmitters and metabolites by gut bacteria, which significantly influence brain function. These findings highlight KD's potential for ASD (77). A case study of a preschool-aged girl with regressive autism showed that MKD (1.5:1 MCTs to carbs/protein) improved seizure control, language, cognition, social interactions, and reduced stereotypical behaviors (78). A recent study showed positive correlations between KD initiation and improved IQ (Intelligence Quotient) in children with ASD, particularly in the Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed subtests of the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) (80). Additionally, KD improved working memory, reference memory, and attention. In a study with 27 participants, over 80% showed favorable outcomes, with no reported detrimental effects (81). Repetitive and restrictive behaviors are common in individuals

with ASD and can significantly impair daily functioning. KD has been investigated as a means to potentially mitigate these behaviours; while studied on 16 environmentally-induced ASD rat models (82). This study was carried out on environmentally-induced ASD-rat models and specifically denoted an improved sociability and a reduction in repetitive behavior while fed with KD (82).

Oxidative Stress

Oxidative stress occurs when ROS exceeds the body's repair capacity, contributing to disorders like ASD (29). Children with ASD have been shown to exhibit elevated levels of oxidative stress markers compared to neurotypical peers (66). Both traditional and modified KDs reduce oxidative stress. Research shows KD lowers oxidative damage in the cytosol and mitochondria, as seen by decreased malondialdehyde (MDA) levels in a mouse autism model (82-85). Additionally, both types of diets significantly lowered levels of 4-hydroxynonenal (4-HNE) and protein carbonyls, which are indicators of oxidative damage to lipids and proteins (85). Mitochondrial dysfunction is frequently observed in individuals with ASD, potentially contributing to behavioral and cognitive symptoms. Both the TKD and MKD have shown promise in alleviating mitochondrial dysfunction, thus supporting patients with ASD (86). Numerous studies demonstrated improvements in mitochondrial respiration and increased activity of mitochondrial complexes in animal models, which leads to enhanced energy production and decreased ROS levels (87, 88).

TKD and MKD are noted for neuroprotective effects, reducing oxidative stress, enhancing mitochondrial activity, and increasing BDNF (Brain-Derived Neurotrophic Factor), which supports neuronal growth. Both diets improve behavior and reduce neuroinflammation in ASD animal models (89). Both TKD and MKD may balance neurotransmitters like GABA and glutamate, often dysregulated in ASD. The elevated mitochondrial ROS production and compromised antioxidant status as has been reportedly found in children with autism, both TKD and MKD could be beneficial for managing ASD symptoms. Both TKD and MKD may reduce oxidative stress, leading to improved mood stability, cognitive and behavioural outcomes, and overall quality of life (90).

Overall Quality of Life in ASD

Quality of life in individuals diagnosed with ASD is mostly influenced by stability of mood and ability to engage in daily activities among many other factors. It can be improved through dietary intervention such as KD. A survey of 114 children by Albers *et al.* (2022) found significant improvements in well-being, mood stability and daily functioning in children with ASD on KD therapy (91). Another case study also supported KD's benefits. A 12-year-old boy showed improved mood, reduced behavioral issues, better sleep and increased participation in school and family life after six months on KD (92). A research using animal models increasingly showed that KD may have clinically beneficial effects in autism. The study from 2013 to 2017 using BTBR, VPA, En2, EL mouse models and Long-Evans rats revealed that KD improved social interactions and reduced repetitive behaviours (93). The study on juvenile and adult mice showed that KD improved vocal communication during male-female interactions, suggesting metabolism-based diets may impact core autism symptoms (94). Another study revealed significant improvements in verbal communication in children being fed with KD. Additionally their parents identified increased vocalizations and better eye contact (95). An observational study demonstrated enhancements in critical non-verbal communication skills, such as gestures and facial expressions during social interactions (92).

A research showed a strong link between cognitive development and ketosis. A recent study on children with ASD illustrated that the initiation time of KD therapy was positively correlated with increased IQ scores, measured by the WISC-IV (Wechsler Intelligence Scale for Children – Fourth Edition) (96). This correlation may be due to KD's impact on brain function and neuroplasticity, enhancing cognitive and language development. Another study acknowledged that KD therapy improved sociability and reduced self-directed repetitive behavior in ASD affected experimental animal models such as the BTBR T+tf/J mouse strain, EL mouse strain and mice with genetic inactivation of the engrailed 2 gene (97). Gogou and Kolis (2018) in their study found that gluten/casein-free modified KD when administered to a 12-year-old boy for 14 months resulted in a remarkable improvement in seizure activity, cognitive ability while reducing repetitive behaviour symptoms (80).

KD was depicted to reduce anxiety by affecting neurotransmitters like GABA and serotonin. KD has been established as a mood-modulating effect and as an antidepressant to treat anxiety and depression (98). Patients with ASD are recognized to have multiple sleep abnormalities including increased latency in onset of sleep and increased number of stage shifts, leading to poor sleep quality (99). However, autistic children following a KD diet showed improvement in sleep structure (improvement of overall sleep quality,

difficulty falling asleep and reduction in night time awakenings) (100).

Lee *et al.* (2018) found that KD may help children with ASD to feel more comfortable socially. After receiving KD (3 months) improvements were seen in CARS-2 (Childhood Autism Rating Scale – Second Edition) items, including imitation, body use, and fear (101). Another study exhibited that an MKD (KD with supplemental medium-chain triglycerides), while continued on 15 children (aged 2 to 17 years) for 3 months has ensured recovery from the core features of ASD such as social sluggishness and fears; thus establishing MKD to be a potential alternative treatment option for ASD (102). Improving behavior is key in managing ASD. KD was shown to enhance behaviour, reduce ADHD, obsessive actions, sleep issues, and seizures by stabilizing GABA, boosting mitochondrial function, and lowering brain inflammation and oxidative stress (98).

Challenges and Limitation in Implementing KD and MKD

Implementing KD and MKD for ASD management poses numerous challenges, such as patients reported the symptoms like diarrhea, vomiting, fatigue, weight loss, and hypoglycemia often limit adherence (103). Nutritional deficiencies, particularly in essential vitamins and minerals like calcium, magnesium, and vitamin D, can impair bone health and neurological function (23, 104, 105). Social and behavioral factors may lead to non-compliance and feelings of isolation in social settings (21, 106). The psychological effects, including mood swings and irritability during the initial stages, add further complications for individuals already struggling with ASD-related symptoms (107). Families face practical challenges, such as frequent medical appointments and increased workloads, along with economic burdens due to specialty foods and supplements (108). While MKD offers a less restrictive alternative, long-term studies on both diets remain limited, necessitating further researches to optimize dietary interventions and guidelines (109, 110).

Diets with Promising Future in the Treatment of ASD

The research put forward that in individuals with ASD, while gluten-free/casein-free and KDs, camel milk, curcumin, probiotics and fermentable foods can play a crucial role in alleviating ASD symptoms; consumption of sugar, additives, pesticides, genetically modified organisms, inorganic processed foods and hard-to-digest starches may aggravate those (109).

Specific Carbohydrate Diet (SCD)

SCD which is more familiar in mitigating symptoms of Crohn's disease, celiac disease, ulcerative colitis, diverticulitis and chronic diarrhea are currently receiving attention for their immense potential in treating neurological disorders as well (107). SCD has been shown to improve GI symptoms, behavior, and nutritional status in a 4-year-old boy with ASD and Fragile X Syndrome (FXS) (103).

Prebiotic and Combined Prebiotics with Probiotics-Rich Diet

A prebiotic is a type of dietary fiber or complex sugar metabolized by gut microbiota, producing short-chain fatty acids, enhances host health by promoting beneficial gut microbiota (98, 99, 111). A pilot study carried out on children aged between 2-11 years and having ASD and GI issues indicated that probiotics (*Bifidobacterium infantis*) combined with the prebiotic Bovine Colostrum Product reduced inflammatory cytokines and improved behaviors and GI symptoms (101). Another study using the prebiotic Bimuno® galactooligosaccharide with a casein- and gluten-free diet in 30 children with ASD showed improvements in social behaviors and reduced abdominal pain during bowel movements, underscoring prebiotics' positive role in ASD (108).

Omega-3 Fatty Acid-rich Diet

Omega-3 fatty acids are vital for growth and bodily functions, prompting numerous studies on their role in alleviating ASD symptoms. In mice and rats, Omega-3 fatty acids improved ultrasonic vocalizations, social discrimination and hyperactivity (96). FXS mice also showed enhanced emotional regulation, social interaction and memory, along with normalization of inflammatory markers (39).

Selenium Supplementation with KD

Selenium deficiency has been found in children with ASD, linked to reduced circulation rather than environmental factors. This deficiency may contribute to low glutathione peroxidase activity in ASD. Studies suggest selenium supplementation to have potential benefits, with some compounds like methyl phenyl selenide showing antidepressant effects in animal studies (86, 87).

Future Prospects of the Study

The future research may focus on integrating findings from various studies on how KD modifies neuronal activity through metabolic changes, thus providing a comprehensive understanding of its potent anti-seizure mechanisms (110). Conducting long-term studies to monitor the sustained effects

of KD in ASD patients over an extended period of time is also the need of the hour. Future researchers may also focus on expanding clinical trials by including diverse populations and age groups to validate the efficacy and safety of KD across different demographics (8). Exploring the potential of combining KD with other therapeutic interventions such as behavioral therapy and/or pharmacological treatments, to enhance overall treatment outcomes of ASD can be another interesting research domain for future researchers. Martin *et al.* (2016) in a separate study has mentioned that MAD-KD, a more palatable diet than classical KD may have a similar effect on seizure control compared to the later; however this assumption requires further investigation (110)**.** The current authors also suggest framing clinical guidelines and policies for implementation of KD as an alternative therapeutic measure for treating ASD and related neurological conditions, as indicated by Kossof *et al*. (2009) (19) as well. KD shows promise in treating epilepsy in infants and toddlers, but a well-designed RCT (Randomized Controlled Trial) is needed to assess its age-specific efficacy. Further researches on its long-term effectiveness in infants are required (110).

Limitation of the Review

This review has only included studies published in English and did not include unpublished data. This study is more focused on the comparative evaluation of KD and MKD; therefore, the duration and the side effects of the diets have not been reviewed. This study has also aimed at the human study model, therefore the animal model studies are not highlighted. Many of the human trials reviewed involve small cohorts, therefore limited the interpretation of data.

Conclusion

Both the KD and its MKDs offer unique promise in supporting individuals with ASD. These dietary approaches may influence brain function, neurotransmitter balance, and metabolic pathways as key areas linked to ASD symptoms. While both forms show potential for enhancing cognitive behavior and improving quality of life, the MKDs stands out for its flexibility and long-term sustainability. Unlike the traditional KD, MKDs typically allow more carbohydrates and proteins, and calorie intake is less tightly regulated. This makes them easier to follow, especially over extended periods. Additionally, the more flexible structure of MKDs, which allows greater freedom in meal timing and carbohydrate choices, can help reduce dietary stress and make it easier for both individuals and caregivers to maintain adherence. Despite these encouraging signs, more comprehensive researches, especially large-scale clinical trials, are crucial. Such studies are needed to uncover exactly how these diets exert their effects and to develop clear, evidence-based guidelines for their implementation in ASD management. In summary, both traditional KD and MKD represent promising therapeutic strategies for ASD. However, further rigorous investigation is essential to confirm their efficacy and ensure their safety over the long term.

Acknowledgement

I would also like to express my gratitude to the Amity Institute of Food Technology, Amity university, Noida, Uttar Pradesh, India and the Department of Food and Nutrition, Brainware University, Kolkata, India for providing library support.

Funding

None.

Authors' Contribution

PD and MV jointly drafted the manuscript and were responsible for the preparation of tables and figures. SP contributed to the ideation, methodological development, and critical revisions of the whole manuscript, including citation of the manuscript. SC critically reviewed and modified the manuscript for intellectual content and clarity. All authors read and approved the final version of the manuscript.

Conflict of Interest

None declared

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