SCRIPTA SCORE Scientific Medical Journal Vol. 7 No. 1 (2025) 071–082

talenta PUBLISHER

SCRIPTA SCORE Scientific Medical Journal
Journal homepage: https://talenta.usu.ac.id/scripta

Review the Potential of Ketogenic Diet and Vitamin B12 Encapsulated Lipid Nanoparticles in Mitochondrial Regulation to Alzheimer's Disease

Reka Febriani [*1], Jaelia Leunufna [1], Nur Ananta Aprilia [1]
[1]*Faculty of Medicine, Pattimura University, Ambon, Indonesia, 97233*
[*]Corresponding Author: fansreka120@gmail.com

ARTICLE INFO

Article history:
Received 28 April 2025
Revised 25 June 2025
Accepted 8 August 2025
Available online 13 August 2024

E-ISSN: 2686-0864
P-ISSN: 2088-8686

How to cite:
Febriani R, Leunufna J, Aprilia NA. Review the Potential of Ketogenic Diet and Vitamin B12 Encapsulated Lipid Nanoparticles in Mitochondrial Regulation to Alzheimer's Disease. SCRIPTA SCORE Sci Med J. 2025 Aug 13;7(1):071-082

https://doi.org/10.32734/scripta.v7i1.20655

ABSTRACT

Background: Alzheimer's disease is the most common form of chronic neurodegenerative syndrome characterized by a decline in two to three major cognitive functions, thus significantly reducing the quality of life of sufferers and their families and this disease has no treatment if it has reached a certain stage and even ends in death. Therefore, preventive approaches are the main focus in the development of alternative therapies, one of which is through modifying dietary patterns that are relevant to daily life. **Objectives:** This literature review aims to analyze the synergistic potential between ketogenic diet and vitamin B12 supplementation encapsulated in lipid nanoparticles in regulating mitochondrial function and inhibiting Alzheimer's disease progression through modulating α-synuclein and amyloid cascade. **Methods:** The review was conducted with a descriptive approach through an online database search conducted by three authors applying inclusion and exclusion criteria resulting in 69 suitable articles. **Result:** The analyzed studies showed that both ketogenic diet and vitamin B12 supplementation have significant effects on mitochondrial regulation and protection of neurons from oxidative stress and chronic inflammation. These interventions also contribute to the modulation of α-synuclein and inhibition of amyloid-beta accumulation, both in preclinical and clinical studies. In addition, the application of lipid nanoparticles improves the biocompatibility and avability of vitamin B12 to reach therapeutic targets. **Conclusion:** the combination of a ketogenic diet and lipid nanoparticle-encapsulated vitamin B12 shows potential as an effective preventive approach to Alzheimer's disease. This study is expected to enrich insights and encourage further clinical research, especially in assessing the long-term effectiveness and potential toxicity of this combination intervention.
Keyword: alpha synuclein, Alzheimer's disease, beta amyloid, lipid nanoparticles, vitamin B12

ABSTRAK

Latar Belakang: Penyakit Alzheimer merupakan bentuk paling umum dari sindrom neurodegeneratif kronis yang ditandai dengan penurunan dua hingga tiga fungsi kognitif utama, sehingga secara signifikan menurunkan kualitas hidup penderita dan keluarganya dan penyakit ini belum memiliki pengobatan jika sudah mencapai stadium tertentu bahkan berakhir pada kematian. Oleh karena itu, pendekatan preventif menjadi fokus utama dalam pengembangan terapi alternatif, salah satunya melalui modifikasi pola diet yang relevan dengan kehidupan sehari-hari. **Tujuan:** Literatur ini bertujuan untuk menganalisis potensi sinergis antara diet ketogenik dan suplementasi vitamin B12 yang dienkapsulasi dalam nanopartikel lipid dalam meregulasi fungsi mitokondria serta menghambat progresivitas penyakit Alzheimer melalui modulasi α-synuclein dan kaskade amiloid. **Methode:** Kajian dilakukan dengan pendekatan deskriptif melalui penelusuran pada database online yang dilakukan oleh tiga penulis dengan menerapkan kriteria inklusi dan eksklusi sehingga diperoleh 69 artikel yang sesuai. **Hasil:** Studi-studi yang dianalisis menunjukkan bahwa baik diet ketogenik maupun suplementasi vitamin B12 memiliki efek signifikan terhadap regulasi mitokondria dan proteksi neuron dari stres oksidatif serta inflamasi kronis. Intervensi ini juga

berkontribusi dalam modulasi α synuclein dan penghambatan akumulasi Beta amyloid, baik dalam penelitian preklinis maupun klinis. Selain itu penerapan nanopartikel lipid meningkatkan biokompabilitas dan avabilitas dari vitamin B12 untuk mencapai target terapi. **Kesimpulan:** Dari hasil kajian ini, kombinasi diet ketogenik dan vitamin B12 enkapsulasi nanopartikel lipid menunjukkan potensi sebagai pendekatan preventif yang efektif terhadap Alzheimer. Kajian ini diharapkan dapat memperkaya wawasan serta mendorong penelitian lanjutan yang lebih mendalam secara klinis, khususnya dalam mengkaji efektivitas jangka panjang dan potensi toksisitas dari kombinasi intervensi ini.
Kata kunci: alpha synuclein, beta amyloid, nanoparticle lipid, penyakit Alzheimer, vitamin B12

1. Introduction

Alzheimer's disease is the most common form of dementia, which is a progressive chronic neurodegenerative syndrome and is characterized by a decline in two or more cognitive domains such as memory, language, executive function, visuospatial, personality, and behavior (Scheltens et al., 2021). This condition causes the loss of an individual's ability to carry out daily activities and has a significant impact on the quality of life of patients and families (Scheltens et al., 2021). In addition to the psychosocial burden, Alzheimer's also poses a large economic burden due to the high cost of medical and long-term care (Paoli et al., 2021; Weller & Budson, 2018). Meta-analysis studies even show that 30-40% of sufferers' family members suffer from severe depression (Kerr et al., 2017). It is also important to be aware that Alzheimer's often does not show typical symptoms in the early stages, so the diagnosis is established late (Scheltens et al., 2021). According to Alzheimer's Disease International, about 50 million people worldwide suffer from Alzheimer's, and this number is predicted to triple to 152 million by 2050 (Scheltens et al., 2021). Meanwhile, in Indonesia, Alzheimer's is suffered by 1.2 million people and this number is expected to increase to 2 million in 2030 and 4 million in 2050 (Kasprata et al, 2018). In 2020, the World Health Organization (WHO) reported that mortality due to Alzheimer's in Indonesia reached 27,054 or 17.01 per 100,000 population (Kasprata et al, 2018). Clinical-based cohort studies in Europe also showed that the average life expectancy of Alzheimer's patients was only about six years after diagnosis was established. Until now, Alzheimer's has not been curable and is one of the leading causes of death in old age (Breijyeh & Karaman, 2020).

The pathogenesis of Alzheimer's is multifactorial, involving various pathological mechanisms such as cortical atrophy, accumulation of β-amyloid plaques and tau proteins, oxidative stress, cholinergic system dysfunction, genetic mutations, and impaired mitochondrial function (Abubakar et al., 2022; Milà-Alomà et al., 2020; Salvadó, Milà-Alomà, et al., 2021). Genetic risk factors, such as the Apolipoprotein E epsilon 4 (APOE ε4) allele, significantly increase susceptibility to the disease (Scheltens et al., 2021). In addition, chronic inflammation has been identified as one of the main mechanisms that exacerbate neuronal damage. The activation of astrocytes, microglia, and the secretion of inflammatory mediators such as cytokines and chemokines leads to nerve inflammation that leads to environmental disturbance of neurons and increased oxidative stress. In fact, β-amyloid itself is known to trigger an inflammatory response (Twarowski & Herbet, 2023). Seeing the high morbidity and mortality rates and the wide impact caused, the development of preventive and therapeutic approaches continues to be developed. One of the approaches that is now widely studied is lifestyle modification, especially through nutritional interventions. Ketosis induced through the ketogenic diet has been shown to have significant neuroprotective effects (Kovács et al., 2021). This effect occurs through increased mitochondrial function, antioxidant and anti-inflammatory activity, modulation of the epigenetic system, and neurotransmitters that have been shown to be able to effectively maintain nutritional ketosis conditions and delay the aging process and the progression of neurodegenerative diseases (Kovács et al., 2021; Morris et al., 2020). Current systematic studies also show that a ketogenic diet may have a protective effect on cognitive function. This diet focuses on the consumption of natural ingredients such as fresh vegetables, seeds, olive oil, nuts, and seafood, by limiting the consumption of dairy products, poultry, red meat, processed foods, and foods high in sugar. Dietary interventions like this are practical, cost-effective, and can reduce dependence on pharmacological therapies (Koppel et al., 2021). Nevertheless, most previous studies have been limited to the evaluation of cognitive function regeneration and have not specifically targeted mitochondrial dysfunction from oxidative stress as the primary root of Alzheimer's pathology. In addition, synergistic combination approaches between dietary modification and molecular therapy are still rarely explored. Therefore, interventions that are able to integrate both approaches in suppressing pathological conditions are needed. One potential strategy is the combination of a ketogenic diet with the administration of vitamin B12 encapsulated in lipid nanoparticles (Gough et al., 2021; Rohmah et al., 2019a; Wilkins & Swerdlow, 2017). The ketogenic diet has been shown to increase mitochondrial efficiency and provide an

alternative energy source in the form of ketone bodies, which can directly reduce the accumulation of β-amyloid. Meanwhile, vitamin B12 plays an important role in homocysteine metabolism as well as neuronal protection, but has low bioavailability when consumed orally. The encapsulation of vitamin B12 in lipid nanoparticles is expected to significantly increase the stability and absorption of the active substance (Alfutaimani et al., 2024a; Cai Shi et al., 2023). This scientific study aims to examine the synergistic potential between the ketogenic diet and the administration of vitamin B12 in the form of encapsulation of lipid nanoparticles in inhibiting the progression of Alzheimer's. The focus of the study is on how this combination can regulate mitochondrial function as well as modulate two main molecular pathways in Alzheimer's, namely α-synuclein expression and β-amyloid formation. By exploring evidence from previous literature, this study is expected to enrich insights into the potential of a combination approach of diet and molecular therapy as a preventive and supportive effort for Alzheimer's.

2. Method

This scientific study is prepared in the form of a narrative review based on the results of analysis of research and previous studies, with a descriptive approach through online literature search. The search was carried out on several databases, including PubMed, Scopus, Google Scholar, and Alzheimer's Disease International. Literature search using keyword combinations: (((((((“Alzheimer disease”) AND (“neurodegeneratif”)) AND (“stres oksidatif”)) AND (“mitokondria”)) AND (“diet ketogenik”)) AND (“vitamin B12”)) AND (“nanopartikel lipid”)) AND (“beta amyloid”)) AND (“alfa-synuclein”)). The search process was conducted in March to collect relevant references related to the topic "Mitochondrial Regulation through a Ketogenic Diet Combined with Encapsulated Vitamin B12 in Lipid Nanoparticles as an Alzheimer's Inhibitor through Synuclein α Modulation and Amyloid Cascades". The criteria include articles with full text, in Indonesian or English, as well as types of clinical, preclinical, systematic, and meta-analysis studies published in the last 10 years. The article must contain interventions in the form of the administration of a ketogenic diet (either through fasting or the regulation of food composition), vitamin B12 supplementation, as well as the application of lipid nanoparticles with results that refer to the regulation and improvement of mitochondrial function from oxidative stress as well as the pathological prevention of Alzheimer's disease through the α pathways of synuclein and β-amyloid. Meanwhile, the exclusion criteria include articles that do not meet the inclusion requirements, such as paid journals (subscription based), articles that are not fully available, and publications that are more than 10 years old. The application of this criterion aims to minimize bias in the studies conducted. From the results of the search and filtering that has been carried out, as many as 69 articles were obtained.

3. Result and Discussion

3.1 Modulation of Amyloid Cascade

Amyloid beta (Aβ) is a short peptide composed of 40 (Aβ40) or 42 (Aβ42) amino acids and is formed through the proteolytic process of amyloid precursor protein (APP) by β- and γ-secretase (Salvadó et al., 2022). Under physiological conditions, APP plays a role in synaptogenesis, synaptic repair, neuronal transport, and regulation of iron metabolism (Salvadó et al., 2022). The synthesis of APP resides in the cell, is post-translationally modified in the endoplasmic reticulum and the Golgi complex, then transported to the cell membrane, where it becomes a substrate for secretase enzymes (Salvadó et al., 2022). APP processing can follow two main pathways, namely non-amyloid and amyloidogenic pathways (Milà-Alomà et al., 2020). In the non-amyloid pathway, the APP protein is cut by α-secretase producing sAPPα and C-Terminal Fragment 83 (CTF83) (Milà-Alomà et al., 2020). Then, CTF83 is cleaved by γ-secretase into p3 peptide and intracellular domain APP (AICD) (Milà-Alomà et al., 2020). Although this pathway was initially thought to be non-Aβ-producing, recent research suggests that p3 may also be involved in Alzheimer's pathology, so the "non-amyloidogenic" status of this pathway is beginning to be questioned and re-examined (Salvadó et al., 2021). In contrast, on the amyloiogenic pathway, APP cutting by β-secretase or Beta-Site APP Cleaving Enzyme (BACE1) results in Soluble Amyloid Precursor Protein-beta (sAPPβ) and CTF99 membrane fragments. (Salvadó et al., 2021b) These fragments are further processed by γ-secretase to form PP Intracellular C-Terminal Domain (AICD) and Aβ. (Salvadó et al., 2021a) The Aβ cascade formed can be exported out of the cell or packaged into a lipid raft. (Milà-Alomà et al., 2020)The Aβ42 variant, which is more hydrophobic, tends to form fibrillary aggregates and form plaques in the extracellular space brain, contributes significantly to Alzheimer's pathology compared to Aβ40. (Milà-Alomà et al., 2020) Abnormalities in this pathway are often associated with genetic mutations in APP and γ-secretase components such as presenilin 1 and 2 (PSEN1 and PSEN2) (Milà-Alomà et al., 2020). The mutation increases the tendency of APP to be processed amyloigenically and increases the production of Aβ42 (Salvadó et al., 2022). brain, contributes significantly to Alzheimer's pathology compared to Aβ40. (Milà-Alomà et al., 2020) Abnormalities in this pathway are often associated with genetic mutations in APP and γ-secretase components such as presenilin 1 and 2 (PSEN1

and PSEN2) (Milà-Alomà et al., 2020). The mutation increases the tendency of APP to be processed amyloigenically and increases the production of Aβ42 (Salvadó et al., 2022). In addition, mitochondrial bioenergetics are also affected. Poorly modulated APP and Aβ can enter the mitochondria, inhibit the import of essential proteins, and disrupt the function of the respiratory chain, ultimately triggering oxidative stress and decreased cellular energy production (Yin et al., 2016; Salvadó et al., 2022). Alpha-synuclein (α-syn) is a small protein that is normally expressed in high amounts in the brain, particularly in the presynaptic terminals of neurons, and plays an important role in the regulation of synaptic vesicles as well as the release of neurotransmitters (Calabresi et al., 2023). Under physiological conditions, α-syn is in a soluble and unstructured form (Calabresi et al., 2023). However, under pathological conditions α-syn can undergo misfolding and aggregation, forming toxic oligomers and amyloid fibrils that are characteristic of Lewy bodies (Kuo et al., 2025). The mechanism of α-syn in triggering inflammation can be seen in (figure 1)

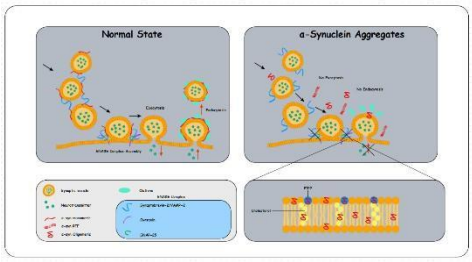

Figure 1. Pathological Mechanisms of α-syn. Source (Kuo et al., 2025)

The presence of α-syn is not only an additional marker of pathology, but also has an active role in exacerbating neurodegenerative pathways dominated by Aβ (Yin et al., 2016; Kuo et al., 2025). Previous studies have shown that α-syn interacts directly with Aβ, forming protein complexes that increase toxicity and accelerate the aggregation of the two (Yin et al., 2016; Salvadó et al., 2022). α-syn oligomers are able to stimulate the amyloid pathway by increasing the activity of β-secretase (BACE1), thereby increasing the processing of APP to Aβ (Yin et al., 2016). This creates conditions that encourage extracellular Aβ buildup in the form of plaques (Yin et al., 2016). In addition, α-syn also affects calcium homeostasis and mitochondrial function (Xu and Pu, 2016). α-syn oligomers can disrupt the integrity of mitochondrial membranes, causing the release of ROS and loss of membrane potential, which ultimately triggers oxidative stress and neuronal apoptosis (Xu and Pu, 2016). On the other hand, Aβ is also known to affect α-syn aggregation and toxicity through phosphorylation, oxidation, and degradation disorders by the lysosome-autophagy system (Xu and Pu, 2016). This interaction relationship strengthens the vicious cycle between two proteins that is the main characteristic of Alzheimer's disease progression (Yin et al., 2016; Salvadó et al., 2022). Dysfunction of protein degradation systems such as proteases and autophagilysosomal pathways is also an important factor in the accumulation of α-syn and Aβ. Under normal conditions, these two proteins are cleared through the mechanism. However, in Alzheimer's this pathway becomes disrupted. As a result, misfolded and aggregated proteins become more and more accumulated, accelerating neuroinflammation and neuronal death.

3.2 Mitochondrial Regulation with the Ketogenic Diet

The brain is an organ that only forms 2% of body weight and is the most intensive in energy needs in the body (Irfannuddin et al., 2021). Not only is glucose a source of energy for the brain, but ketones also hold up to 60% of the brain's energy needs (Irfannuddin et al., 2021). The ketogenic diet is a low-carbohydrate, high-fat diet that encourages the body to produce ketone bodies such as β-hydroxybutyrate (βHB), acetoacetate, and acetone, thus achieving a state of ketosis (Gano, Patel and Rho, 2014). This ketosis gives the body the opportunity to get most of its energy from fat and minimize carbohydrate consumption (Breijyeh and Karaman, 2020; Pietrzak et al., 2022). The macronutrient pattern in a ketogenic diet generally consists of 60-90% fat (usually 70-75%), less than 50 grams of carbohydrates per day (about 5-10% of total calories), and protein as much as 1.0-1.7 grams/kg of body weight (about 20% of total calories) (Morris et al., 2020). mimics the effects of fasting without causing negative impacts, by increasing the oxidation of fatty acids and the use of ketone bodies as the primary energy substrate (Morris et al., 2020). Studies in transgenic mice Green Fluorescent Protein– microtubule-associated protein 1A/1B-light chain 3 (GFP-LC3) showed that fasting for 24-48 hours can increase the number of autophagosomes in cortical neurons (Kephart et al., 2017). In addition, physical activities such as running on wheels also exhibit neuroprotective effects mediated by increased Sirtuin (SIRT3) expression in the hippocampus and cortex (Qiao et al., 2022). Fasting and exercise are known to stimulate mitochondrial biogenesis through the activation of Brain-Derived Neurotrophic Factor (BDNF) and the

regulation of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α), an important pathway in synapse formation and plasticity. In a state of long-term starvation, the brain is able to obtain up to two-thirds of its energy needs from ketone bodies (Brenton et al., 2019; Gough et al., 2021). Ketone bodies can penetrate the blood-brain barrier and are used as an energy source by the cells of the central nervous system (Hernandez et al., 2019; Agnello and Ciaccio, 2022). Through the process of ketolysis, ketone bodies are converted into acetyl-CoA which enters the Tricarboxylic Acid Cycle (TCA) to produce energy (Greco et al., 2016). The ketogenic diet plays a major role in regulating mitochondrial function and dynamics, especially in the context of neurodegenerative diseases such as Alzheimer's (Gano, Patel and Rho, 2014; Greco et al., 2016). Mitochondria, as centers for energy production through oxidative phosphorylation, are particularly susceptible to damage due to chronic oxidative stress (Greco et al., 2016). The production of ketone bodies from the ketogenic diet replaces glucose as the primary source of energy in the brain, and triggers significant molecular as well as epigenetic changes (Greco et al., 2016; Mary et al., 2023). From a molecular mechanism, βHB can increase the expression of PGC-1α, a key transcriptional coactivator in mitochondrial biogenesis (Mary et al., 2023; Paoli and Cerullo, 2023). PGC-1α works in tandem with Nuclear Respiratory Factor (NRF1 and NRF2) in activating mitochondrial genes such as Mitochondrial Transcription Factor A (TFAM), which regulates mitochondrial DNA replication and transcription (Dewi Maharani et al., n.d.; Yin et al., 2016; Gough et al., 2021). Preclinical evidence suggests that mice on a ketogenic diet experienced increased expression of PGC-1α and NRF2, which in turn increased the amount and efficiency of mitochondrial respiration, particularly in the hippocampus of brain regions that play an important role in memory and cognition (Qiao et al., 2022). Activation of SIRT1 and AMP-Activated Protein Kinas (AMPK) amplifies this effect (Desjardins et al., 2022). The ketone body induces SIRT1, a deacetylase enzyme dependent on Nicotinamide Adenine Dinucleotide (NAD+), which activates PGC-1α and protects cells from oxidative stress by increasing the expression of antioxidant genes such as Superoxide Dismutase 2 (SOD2) and catalase (Gano, Patel and Rho, 2014; Kerr et al., 2017; Seira et al., 2021; Mary et al., 2023). Activation of AMPK, as an energy sensor, responds to an increase in the ratio of Adenosine Monophosphate/Adenosine Triphosphate (AMP/ATP) due to glucose deficit by inducing metabolic adaptations, including fatty acid oxidation and mitofagi (Gano, Patel and Rho, 2014). mitofagi is a process of mitochondrial degradation that is damaged and enhanced under ketogenic diet conditions (Gano, Patel and Rho, 2014; Greco et al., 2016). This is important because the accumulation of dysfunctional mitochondria can increase the production (Reactive Oxidative Stress) of ROS and activate the cell death pathway (Greco et al., 2016). Ketogenic diets have been shown to increase the expression of PTEN-Induced Kinase 1 (PINK1) and Parkin, two major regulators of mitophagy, which play a role in keeping only healthy mitochondria within neurons (Gano, Patel and Rho, 2014; Mary et al., 2023). In animal models, this diet reduces the accumulation of damaged mitochondria and improves energy homeostasis in aging brains (Stumpf et al., 2019). The effects of ketogenesis on mitochondria can be seen in (figure 2)

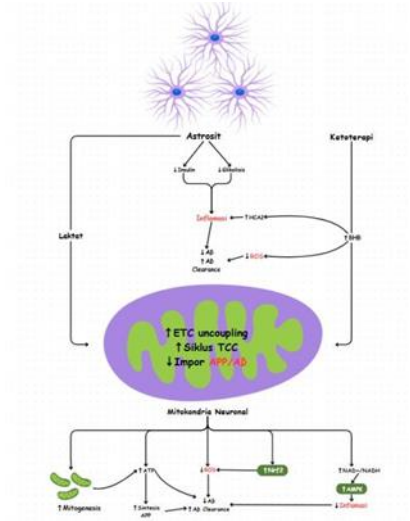

Figure 2. Effects of ketogenesis on mitochondria. Source (Greco et al., 2016)

In the aspect of oxidative stress, βHB has direct and indirect antioxidant properties (Greco et al., 2016; Pietrzak et al., 2022). Directly, it increases the efficiency of the electron transport chain and lowers electron leakage (Desjardins et al., 2022; Wesół- Kucharska et al., 2024). Indirectly, βHB inhibits histone deacetylase (HDAC), which leads to increased expression of protective genes such as NRF2 and Forkhead box O3a (FOXO3a) (Yarar-Fisher et al., 2021; Desjardins et al., 2022). The NRF2 gene is an important transcription factor that regulates antioxidant systems and detoxifying enzymes (Desjardins et al., 2022). Activation of this pathway

has been shown to lower oxidative stress and β-amyloid aggregation in Alzheimer's mouse models (Desjardins et al., 2022). The ketogenic diet also regulates inflammatory mechanisms, both at the central and peripheral levels (Cooper et al., 2018; Yarar-Fisher et al., 2021). It has been shown that this diet reduces the activation of microglia and decreases the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and Tumor Necrosis Factor-alpha (TNF-α) in the hippocampus (Cooper et al., 2018). In addition, this diet suppresses the inflammatory pathway Cyclooxygenase-2 (COX-2) through the activation of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) Astrocytes, which are also capable of producing ketone bodies and contribute to this neuroprotective effect (Miller et al., n.d.; Parry et al., 2018; Qiao et al., 2022). Ketosis is also known to improve the integrity of the brain's blood barrier by increasing the expression of connectin-43 (Cx43), monocarboxylate transporter (MCT), and Glucose Transporter (GLUT) (Newport et al., 2015; Michalczyk et al., 2020). The ketogenic diet also supports the elimination of amyloid plaques through increased transport proteins such as Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1), P-glycoprotein (P-gp), and Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) (Stumpf et al., 2019; Taylor et al., 2022). Preclinical research shows an increase in mitochondrial density and integrity in cortical neurons as well as an increase in cellular energy reserves characterized by NAD+/NADH ratios and ATP levels (Seira et al., 2021). Mice on a ketogenic diet showed improved cognitive function, resistance to glutamate excitotoxicity, as well as decreased activation of microglia and proinflammatory cytokines (Seira et al., 2021). The mechanism of potential effects on the neurological system can be seen in (figure 3)

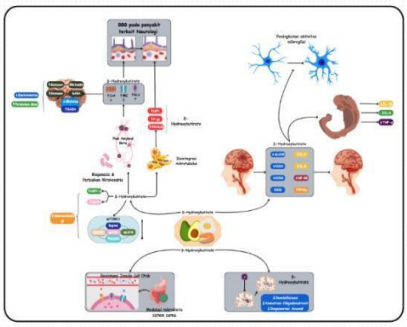

Figure 3. Mechanism of the Ketogenic Effect. Source (Taylor et al., 2022)

Clinical evidence supports these findings. Studies in patients with mild cognitive impairment (MCI) and Alzheimer's show that medium-chain triglyceride (MCT) supplementation, which is converted to ketones by the liver, increases blood βHB levels and improves episodic memory and attention (Juby, Blackburn and Mager, 2022). The study of Krikorian et al showed improved verbal memory performance after 6 weeks of a low-carb diet (Krikorian et al., 2021). Other clinical studies have shown that ketones may replace glucose as a source of brain energy in Alzheimer's patients, who have impaired glucose metabolism (Kovács, Brunner and Ari, 2021). A randomized controlled trial study in 2021 compared the ketogenic diet with a low-fat diet in Alzheimer's patients, and showed an improvement in cognitive function of 2.12 ± 8.70 points on the ACE-III scale as well as an improvement in daily function of 3.12 ± 5.01 points (Guevara-Cruz et al., 2024). A preclinical study by Greco et al showed that administering ketones to male mice for 35 days post-injury increased the expression of antioxidant proteins and SOD, preventing mitochondrial dysfunction due to oxidative stress (Greco et al., 2016). A 2020 meta-analysis of 932 participants also supports the benefits of this diet (Malinowska and Żendzian- Piotrowska, 2024). Side effects such as diarrhea, constipation, and vomiting have been reported, but are generally mild (Malinowska and Żendzian- Piotrowska, 2024). Other effects such as decreased body mass, nausea, and lethargy are rare (Malinowska and Żendzian-Piotrowska, 2024). In a randomized trial in Alzheimer's patients, no significant side effects were found after a 12-week ketogenic diet intervention on the expression of synaptic signaling genes in Cornu Ammonis (CA1, CA3), and the dentate gyrus analyzed using Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR) (Di Lorenzo et al., 2019). The ketogenic diet affects the expression of genes in CA3 and the dentate gyrus, which are involved in the regulation of glutamate and synapse plasticity (Di Lorenzo et al., 2019). Thus, the ketogenic diet regulates mitochondrial function through molecular and epigenetic pathways such as PGC-1α, SIRT1, AMPK, as well as the antioxidant pathways NRF2 and FOXO3a. This diet promotes mitochondrial biogenesis, strengthens mitophagy, lowers oxidative stress, and provides a stable alternative source of energy.

3.3 The Role of Vitamin B12 in Mitochondrial Regulation

Vitamin B12, or cobalamin, is a water-soluble vitamin that plays a very important role in various biological processes of the body, especially those related to the functioning of the central nervous system and energy

metabolism at the cellular level (El-Mezayen, Abd el Moneim and El-Rewini, 2022). Adults are recommended to get a daily intake of 2.4 μg. The average daily meal contains 3-30 μg and is absorbed by the gastrointestinal 2-3 μg (El-Mezayen, Abd el Moneim and El-Rewini, 2022). Vitamin B12 in the body is necessary to carry out two important enzymatic reactions (El- Mezayen, Abd el Moneim and El- Rewini, 2022). First, the conversion of homocysteine to methionine through the enzyme methionine synthase which uses methylcobalamin as a cofactor (Issac et al., 2015). Second, the conversion of methylmalonyl-CoA to succinyl-CoA by adenosylolin-dependent methylmalonyl-CoA mutase (Issac et al., 2015). These two reactions are essential for the integrity of cellular function, particularly in terms of mitochondrial maintenance and neuronal activity (Lam, Kervin and Tanis, 2021). Vitamin B12 deficiency results in disruption of both pathways, which is clinically characterized by increased levels of homocysteine and methylmalonate in the blood (Lam, Kervin and Tanis, 2021). The accumulation of homocysteine causes significant disruption in the nervous system because it is neurotoxic, homocysteine triggers increased oxidative stress and activates apoptotic pathways through disruption of the redox balance of cells (Lam, Kervin and Tanis, 2021). Homocysteine also causes an increase in ROS, DNA damage, as well as affects the integrity of the mitochondrial membrane. On the other hand, increased methylmalonate due to impaired Minichromosome Maintenance (MCM) function contributes to mitochondrial dysfunction by inhibiting the work of complexes I and II of the electron transport chain, thereby decreasing ATP production and increasing ROS (Issac et al., 2015; An et al., 2019). These two toxicity pathways place vitamin B12 as an important nutrient in maintaining mitochondrial stability and function (An et al., 2019). Mitochondria themselves act as a very vital energy generating center for neurons (Gowda, Reddy and Kumar, 2022). Unlike other cells, neurons have very high energy requirements and rely heavily on the continued production of ATP through oxidative phosphorylation to maintain membrane potential, regulate synaptic transmission, and support the growth and repair of axonal structures (Gano, Patel and Rho, 2014). When vitamin B12 levels in the body are inadequate, various studies show that mitochondrial function is significantly impaired (Park, Kang and Sol Kim, 2022; Sharma and Aran, 2025). Depolarization of mitochondrial membranes, release of cytochrome c, and activation of kaspases that mark neuronal apoptosis were found to be higher in B12 deficiency conditions (Issac et al., 2015). In contrast, methylcobalamin supplementation has been shown to stabilize mitochondrial membranes, reduce cytochrome c release, and increase the expression of anti-apoptotic proteins such as B-cell Lymphoma 2 (Bcl-2), thereby preventing neuronal cell death induced by oxidative stress (Issac et al., 2015). In addition to its protective function against mitochondria, vitamin B12 also has a significant regenerative role in the nervous system (An et al., 2019). Several animal studies have shown that the administration of methylcobalamin is able to accelerate axonal regeneration and improve nerve conduction function in cases of peripheral nerve injury (An et al., 2019). This effect has to do not only with increased mitochondrial density and activity, but also through modulation of gene expression that favors neuronal growth. (An et al., 2019) For example, methylcobalamin is known to increase the expression of neurodegenerative factor (NGF) nerve growth factor, as well as activate the Extracellular signal-Regulated Kinases 1 and 2 (ERK1/2) signaling pathway that play a role in neuronal proliferation and survival (An et al., 2019). The ERK1/2 pathway is also known to inhibit the activation of kaspase 3, an important marker of the apoptosis process. Thus, vitamin B12 actively promotes the repair of nerve structure and function through complex molecular mechanisms (An et al., 2019; Lam, Kervin and Tanis, 2021). In addition, the influence of vitamin B12 on the nervous system is not only limited to peripheral injuries, but also includes neurodegenerative diseases such as Alzheimer's (El-Mezayen, Abd el Moneim and El-Rewini, 2022). Decreased B12 levels in Alzheimer's patients are often found in conjunction with increased homocysteine and decreased methionine and SAM (S-adenosylmethionine), which have a direct impact on impaired DNA and protein methylation, including tofu protein (El-Mezayen, Abd el Moneim and El-Rewini, 2022; Park, Kang and Sol Kim, 2022). Preclinical studies show that B12 supplementation can decrease the formation of β-amyloid plaques and prevent hyperphosphorylation of tau, two hallmarks of Alzheimer's pathology (Park, Kang and Sol Kim, 2022). This effect is believed to occur through the restoration of mitochondrial function, a decrease in ROS, and a reduction in oxidative DNA damage in nerve cells (Park, Kang and Sol Kim, 2022). The role of vitamin B12 in neurodegenerative diseases can be seen in (figure 4)

SCRIPTA SCORE Scientific Medical Journal Vol. 7 No. 1 (2025) 071–082

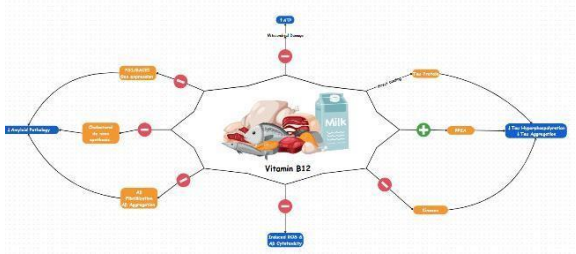

Figure 4. The Role of Vitamin B12. Source (El- Mezayen et al., 2022)

Of the several studies that vitamin B deficiency can increase the accumulation of β-amyloid, a study with trial mice in 2020 showed that dysfunction of the intestinal epithelial barrier (IEB) or intestinal epithelial barrier can occur before the accumulation of β-amyloid in the brain or injury of white matter in the central nervous system (An et al., 2019). This is proven through a study on six-month-old transgenic Tg2576 mice that are still in the pre-symptomatic stage (An et al., 2019). At that age, the mice did not show the presence of β-amyloid plaques in the subcucumber and hippocampus, kinase) in regulating cellular functions (i.e. proliferation, differentiation, survival and synaptic plasticity, in contrast to the 15-month-old transgenic mice that had experienced significant plaque formation, This study also found that in pre-symptomatic Tg2576 mice there was a significant decrease in the expression of the cubulin gene, which is a transporter that plays an important role in the absorption of vitamin B12 in the ileum (An et al., 2019). A 2021 preclinical study utilized Caenorhabditis elegans as an alternative animal model to examine the impact of vitamin B12 on β-amyloid toxicity (Andra et al., 2021). In this model, the C. elegans worm is transgenically engineered to express human Aβ42 peptide in the muscles of its body wall The expression causes pathological symptoms that resemble Alzheimer's disease, such as decreased ATP levels, disruption of mitochondrial structure, increased oxidative stress, and progressive paralysis that occurs over time (Andra et al., 2021). Other results showed that C. elegans worms that did not receive vitamin B12 supplementation experienced paralysis faster and more severely compared to the group that received regular vitamin B12 intake (Cai Shi et al., 2023). Vitamin B12 supplementation has been shown to delay the onset of Aβ42-induced paris (Cai Shi et al., 2023). In addition, vitamin B12 also plays a role in maintaining the integrity of the nerve cell genome through its role in the methylation cycle (An et al., 2019). Methionine deficiency due to B12 deficiency causes disruption in the formation of SAM, a universal methyl donor used in the methylation of DNA, RNA (An et al., 2019). This imbalance interferes with the expression of genes that play a role in neuronal function and synaptic plasticity, and can increase susceptibility to environmental stress proteins (Issac et al., 2015). Vitamin B12 can also inhibit the activation of microglia inflammatory pathways that can exacerbate neuronal damage (Chen et al., 2021; Kaszyńska, 2024). Therefore, vitamin B12 has an important role in regulating mitochondria plus antioxidant and antineudegenerative properties to prevent the formation of amyloid plaques and oxidative stress.

3.4 Encapsulation of Vitamin B12 in Lipid Nanoparticles

Vitamin B12 is a water-soluble compound with a very complex chemical structure (Lam, Kervin and Tanis, 2021). In the human body, the absorption of this vitamin does not occur directly, but must go through a process that involves the release of food-binding proteins by gastric enzymes, as well as gradual binding by transport proteins such as haptokin, intrinsic factors, and transcobalamin (Lam, Kervin and Tanis, 2021).

This long physiological process, coupled with the soluble and quickly eliminated properties of vitamin B12 from the body, leads to low bioavailability (bioavailability) of this vitamin (Kaszyńska, 2024). To overcome these limitations, nanotechnology-based approaches have begun to be developed, one of which is the lipid nanoparticle encapsulation method (Alfutaimani et al., 2024). The application of lipid nanoparticles as an encapsulated vitamin B12 delivery system aims to protect the vitamin from degradation during the digestive process and improve its ability to penetrate target tissues (Alfutaimani et al., 2024; Mindiarto, Jafar and Putriyanti, 2024). Lipid nanoparticles are nano-sized colloidal structures formed from natural lipids and are biocompatible. Due to its ability to envelop water-soluble compounds in aqueous spaces within its lipid structure, this system is ideal for bringing vitamin B12 into the body more stably and efficiently (Wang et al., 2016; Rohmah et al., 2019). In addition to improving the stability of the compound, this method also allows for the release of vitamins slowly and controllably, so that the concentration of vitamins in the blood can be maintained over a longer period of time (Wang et al., 2016 application of lipid nanoparticle encapsulation systems can be seen in (figure 5)

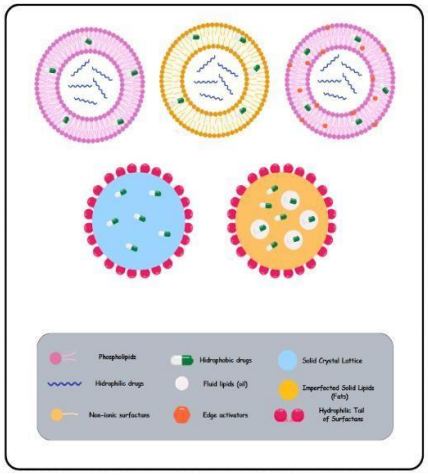

Figure 5. Lipid nanoparticles. Source (Wang et al., 2016)

A widely developed lipid is Solid Lipid Nanoparticles (SLN) which are composed of solid lipids and have a particle size in the range of 50-500 nanometers (Rohmah et al, 2019). This type of nanoparticle provides space for the content of active compounds such as vitamin B12 to be stored in its lipid structure without causing toxicity, as it uses physiological lipids that are safe and biodegradable in the body (Wang et al., 2018; Mindiarto, Jafar and Putriyanti, 2024). By using surfactants as stabilizers, SLN can maintain its shape and stability at both room temperature and body temperature, making it suitable for large-scale storage and distribution (Alfutaimani et al., 2024). In addition to SLN, the latest innovation presents Nanostructured Lipid Carriers (NLC), which is a development of SLN with a mixed composition of solid lipids and liquid lipids (Alfutaimani et al., 2024). This modification aims to improve the absorption efficiency of the active substance as well as improve the drug release profile (Wang et al., 2016). The advantage of NLC lies in its flexibility in accommodating different types of compounds, including vitamin B12, as well as its potential in breaking through biological barriers such as the brain's blood barrier, which is important for the therapy of neurodegenerative diseases.

4. Conclusion

Based on the literature reviewed, the ketogenic diet and vitamin B12 supplementation encapsulated in lipid nanoparticles emerged as an intervention approach that is considered relevant to modern lifestyles and can be applied as a preventive effort from young to adulthood. The combined application of the two is supported by an optimal supplementation delivery system in the form of lipid nanoparticles. This effectiveness is supported by the antioxidant properties of the ketone diet and vitamin B12 which are able to suppress oxidative stress and improve cellular function. A number of preclinical and clinical studies have shown significant results against the biomolecular modulation involved in neurodegeneration. However, this study has limitations where there are not many studies that directly combine ketogenic dietary interventions and vitamin B12 in one integrated and clinical research design. Therefore**,** further large-scale, controlled, and long-term research is needed confirming the effectiveness for and safety of these combinations of therapies clinically and the toxicity that is possible if the two therapies are combined. It is hoped that this study will not only add to the reader's insights, but also become the initial basis for further research on the development of applicability in clinical interventions and for the prevention of Alzheimer's disease both in Indonesia and the world.

References

[1] Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer’s disease. Vol. 397, The Lancet. Elsevier B.V.; 2021. p. 1577–90.
[2] Paoli A, Cerullo G. Investigating the Link between Ketogenic Diet, NAFLD, Mitochondria, and Oxidative Stress: A Narrative Review. Vol. 12, Antioxidants. MDPI; 2023.
[3] Weller J, Budson A. Current understanding of Alzheimer’s disease diagnosis and treatment. Vol. 7, F1000Research. F1000 Research Ltd; 2018.
[4] Kerr JS, Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA, et al. Mitophagy and Alzheimer’s Disease: Cellular and Molecular Mechanisms. Vol. 40, Trends in Neurosciences. Elsevier Ltd; 2017. p. 151–66.
[5] Novan Kasprata H, Harahap HS. TINJAUAN PUSTAKA: DIAGNOSIS DAN TATALAKSANA DEMENSIA ALZHEIMER [Internet]. 2018. Vol. 10, Jurnal Ilmu Kedokteran dan Kesehatan. Available from: http://ejurnalmalahayati.ac.id/index.php/kesehatan

[6] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Vol. 25, Molecules. MDPI; 2020.
[7] Abubakar MB, Sanusi KO, Ugusman A, Mohamed W, Kamal H, Ibrahim NH, et al. Alzheimer's Disease: An Update and Insights Into Pathophysiology. Vol. 14, Frontiers in Aging Neuroscience. Frontiers Media S.A.; 2022.
[8] Salvadó G, Milà-Alomà M, Shekari M, Minguillon C, Fauria K, Niñerola-Baizán A, et al. Cerebral amyloid-β load is associated with neurodegeneration and gliosis: Mediation by p-tau and interactions with risk factors early in the Alzheimer's continuum. Alzheimer's and Dementia. 2021 May 1;17(5):788–800.
[9] Milà-Alomà M, Salvadó G, Gispert JD, Vilor-Tejedor N, Grau-Rivera O, Sala-Vila A, et al. Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's continuum. Alzheimer's and Dementia. 2020 Oct 1;16(10):1358–71.
[10] Twarowski B, Herbet M. Inflammatory Processes in Alzheimer's Disease—Pathomechanism, Diagnosis and Treatment: A Review. Vol. 24, International Journal of Molecular Sciences. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
[11] Kovács Z, Brunner B, Ari C. Beneficial effects of exogenous ketogenic supplements on aging processes and age-related neurodegenerative diseases. Vol. 13, Nutrients. MDPI AG; 2021.
[12] Morris G, Maes M, Berk M, Carvalho AF, Puri BK. Nutritional ketosis as an intervention to relieve astrogliosis: Possible therapeutic applications in the treatment of neurodegenerative and neuroprogressive disorders. European Psychiatry. 2020;63(1).
[13] Koppel SJ, Pei D, Wilkins HM, Weidling IW, Wang X, Menta BW, et al. A ketogenic diet differentially affects neuron and astrocyte transcription. J Neurochem. 2021 Jun 1;157(6):1930–45.
[14] Gough SM, Casella A, Ortega KJ, Hackam AS. Neuroprotection by the Ketogenic Diet: Evidence and Controversies. Vol. 8, Frontiers in Nutrition. Frontiers Media S.A.; 2021.
[15] Rohmah M, Raharjo S, Hidayat C, Martien R. Formulasi dan Stabilitas Nanostructured Lipid Carrier dari Campuran Fraksi Stearin dan Olein Minyak Kelapa Sawit. Jurnal Aplikasi Teknologi Pangan. 2019 Feb 28;8(1).
[16] Wilkins HM, Swerdlow RH. Amyloid precursor protein processing and bioenergetics. Vol. 133, Brain Research Bulletin. Elsevier Inc.; 2017. p. 71–9.
[17] Alfutaimani AS, Alharbi NK, S. Alahmari A, A. Alqabbani A, Aldayel AM. Exploring the landscape of Lipid Nanoparticles (LNPs): A comprehensive review of LNPs types and biological sources of lipids. Vol. 8, International Journal of Pharmaceutics: X. Elsevier B.V.; 2024.
[18] Cai Shi D, Long C, Vardeman E, Kennelly EJ, Lawton MA, Di R. Potential Anti-Alzheimer Properties of Mogrosides in Vitamin B12-Deficient Caenorhabditis elegans. Molecules. 2023 Feb 1;28(4).
[19] Salvadó G, Milà-Alomà M, Shekari M, Operto G, Sánchez-Benavides G, Cacciaglia R, et al. Structural, metabolic and cognitive characteristics of cognitively unimpaired subjects with mismatching β-amyloid biomarkers. Alzheimer's & Dementia [Internet]. 2021 Dec;17(S4). Available from: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.052507
[20] Yin F, Sancheti H, Patil I, Cadenas E. Energy metabolism and inflammation in brain aging and Alzheimer's disease. Vol. 100, Free Radical Biology and Medicine. Elsevier Inc.; 2016. p. 108–22.
[21] Calabresi P, Di Lazzaro G, Marino G, Campanelli F, Ghiglieri V. Advances in understanding the function of alpha-synuclein: implications for Parkinson's disease. Brain. 2023 Sep 1;146(9):3587–97.
[22] Kuo G, Kumbhar R, Blair W, Dawson VL, Dawson TM, Mao X. Emerging targets of α-synuclein spreading in α-synucleinopathies: a review of mechanistic pathways and interventions. Mol Neurodegener [Internet]. 2025 Jan 23;20(1):10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/39849529
[23] Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Vol. 14, Translational Oncology. Neoplasia Press, Inc.; 2021.
[24] Xu S, Yang K, Li R, Zhang L. Mrna vaccine era mechanisms, drug platform and clinical prospection. Vol. 21, International Journal of Molecular Sciences. MDPI AG; 2020. p. 1–35.
[25] Irfannuddin I, Sarahdeaz SFP, Murti K, Santoso B, Koibuchi N. The effect of ketogenic diets on neurogenesis and apoptosis in the dentate gyrus of the male rat hippocampus. Journal of Physiological Sciences. 2021 Dec 1;71(1).
[26] Gano LB, Patel M, Rho JM. Ketogenic diets, mitochondria, and neurological diseases. Vol. 55, Journal of Lipid Research. American Society for Biochemistry and Molecular Biology Inc.; 2014. p. 2211–28.
[27] Pietrzak D, Kasperek K, Rękawek P, Piątkowska-Chmiel I. The Therapeutic Role of Ketogenic Diet in Neurological Disorders. Vol. 14, Nutrients. MDPI; 2022.
[28] Parry HA, Kephart WC, Mumford PW, Romero MA, Mobley CB, Zhang Y, et al. Ketogenic diet increases mitochondria volume in the liver and skeletal muscle without altering oxidative stress markers in rats. Heliyon [Internet]. 2018;4:975. Available from: http://creativecommons.org/licenses/by/4.0/

[29] Qiao Q, Qu Z, Tian S, Cao H, Zhang Y, Sun C, et al. Ketogenic Diet Alleviates Hippocampal Neurodegeneration Possibly via ASIC1a and the Mitochondria-Mediated Apoptotic Pathway in a Rat Model of Temporal Lobe Epilepsy. Neuropsychiatr Dis Treat. 2022;18:2181–98.
[30] Brenton JN, Banwell B, Christina Bergqvist AG, Lehner-Gulotta D, Gampper L, Leytham E, et al. Pilot study of a ketogenic diet in relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm. 2019 Jul 1;6(4).
[31] Hernandez AR, Hernandez CM, Truckenbrod LM, Campos KT, McQuail JA, Bizon JL, et al. Age and Ketogenic Diet Have Dissociable Effects on Synapse-Related Gene Expression Between Hippocampal Subregions. Front Aging Neurosci. 2019 Sep 13;11.
[32] Agnello L, Ciaccio M. Neurodegenerative Diseases: From Molecular Basis to Therapy. Vol. 23, International Journal of Molecular Sciences. MDPI; 2022.
[33] Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. Journal of Cerebral Blood Flow and Metabolism. 2016 Sep 1;36(9):1603–13.
[34] Mary A, Eysert F, Checler F, Chami M. Mitophagy in Alzheimer's disease: Molecular defects and therapeutic approaches. Vol. 28, Molecular Psychiatry. Springer Nature; 2023. p. 202–16.
[35] Dewi Maharani N, Halimi RA, Mafiana R, Gaus S. Disfungsi Kognitif Post Operatif pada Geriatri.
[36] Desjardins EM, Smith BK, Day EA, Ducommun S, Sanders MJ, Nederveen JP, et al. The phosphorylation of AMPKβ1 is critical for increasing autophagy and maintaining mitochondrial homeostasis in response to fatty acids. Proc Natl Acad Sci U S A. 2022 Nov 29;119(48).
[37] Seira O, Kolehmainen K, Liu J, Streijger F, Haegert A, Lebihan S, et al. Ketogenesis controls mitochondrial gene expression and rescues mitochondrial bioenergetics after cervical spinal cord injury in rats. Sci Rep. 2021 Dec 1;11(1).
[38] Stumpf SK, Berghoff SA, Trevisiol A, Spieth L, Düking T, Schneider L V., et al. Ketogenic diet ameliorates axonal defects and promotes myelination in Pelizaeus–Merzbacher disease. Acta Neuropathol. 2019 Jul 1;138(1):147–61.
[39] Wesół-Kucharska D, Greczan M, Kaczor M, Ehmke vel Emczyńska-Seliga E, Hajdacka M, Czekuć-Kryśkiewicz E, et al. Efficacy and Safety of Ketogenic Diet Treatment in Pediatric Patients with Mitochondrial Disease. Nutrients. 2024 Mar 1;16(6).
[40] Yarar-Fisher C, Li J, Womack ED, Alharbi A, Seira O, Kolehmainen KL, et al. Ketogenic regimens for acute neurotraumatic events. Vol. 70, Current Opinion in Biotechnology. Elsevier Ltd; 2021. p. 68–74.
[41] Cooper MA, McCoin C, Pei D, Thyfault JP, Koestler D, Wright DE. Reduced mitochondrial reactive oxygen species production in peripheral nerves of mice fed a ketogenic diet. Exp Physiol. 2018 Sep 1;103(9):1206–12.
[42] Miller VM, Sorabella RA, Padilla LA, Sollie Z, Izima C, Johnson WH, et al. Health-Related Quality of Life After Single Ventricle Palliation or Tetralogy of Fallot Repair. Pediatr Cardiol. 2023;44(1).
[43] Newport MT, Vanitallie TB, Kashiwaya Y, King MT, Veech RL. A new way to produce hyperketonemia: Use of ketone ester in a case of Alzheimer's disease. Alzheimer's and Dementia. 2015;11(1):99–103.
[44] Michalczyk MM, Klonek G, Maszczyk A, Zajac A. The effects of a low calorie ketogenic diet on glycaemic control variables in hyperinsulinemic overweight/obese females. Nutrients. 2020 Jun 1;12(6):1–14.
[45] Taylor MK, Sullivan DK, Keller JE, Burns JM, Swerdlow RH. Potential for Ketotherapies as Amyloid-Regulating Treatment in Individuals at Risk for Alzheimer's Disease. Vol. 16, Frontiers in Neuroscience. Frontiers Media S.A.; 2022.
[46] Juby AG, Blackburn TE, Mager DR. Use of medium chain triglyceride (MCT) oil in subjects with Alzheimer's disease: A randomized, double-blind, placebo-controlled, crossover study, with an open-label extension. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2022;8(1).
[47] Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. Neurobiol Aging. 2012;33(2):425.e19-425.e27.
[48] Guevara-Cruz M, Hernández-Gómez KG, Condado-Huerta C, González-Salazar LE, Peña-Flores AK, Pichardo-Ontiveros E, et al. Intermittent fasting, calorie restriction, and a ketogenic diet improve mitochondrial function by reducing lipopolysaccharide signaling in monocytes during obesity: A randomized clinical trial. Clinical Nutrition. 2024 Aug 1;43(8):1914–28.
[49] Malinowska D, Żendzian-Piotrowska M. Ketogenic Diet: A Review of Composition Diversity, Mechanism of Action and Clinical Application. Suzuki T, editor. J Nutr Metab [Internet]. 2024 Jan 18;2024(1). Available from: https://onlinelibrary.wiley.com/doi/10.1155/2024/6666171

[50] Di Lorenzo C, Pinto A, Ienca R, Coppola G, Sirianni G, Di Lorenzo G, et al. A randomized double-blind, cross-over trial of very low-calorie diet in overweight migraine patients: A possible role for ketones? Nutrients. 2019;11(8).
[51] El-Mezayen NS, Abd el Moneim RA, El-Rewini SH. Vitamin B12 as a cholinergic system modulator and blood brain barrier integrity restorer in Alzheimer's disease. European Journal of Pharmaceutical Sciences. 2022 Jul 1;174.
[52] Issac T, Soundarya S, Christopher R, Chandra S. Vitamin B12 deficiency: An important reversible co-morbidity in neuropsychiatric manifestations. Indian J Psychol Med. 2015 Jan 1;37(1):26–9.
[53] Lam AB, Kervin K, Tanis JE. Vitamin B12 impacts amyloid beta-induced proteotoxicity by regulating the methionine/S-adenosylmethionine cycle. Cell Rep. 2021 Sep 28;36(13).
[54] Gowda P, Reddy PH, Kumar S. Deregulated mitochondrial microRNAs in Alzheimer's disease: Focus on synapse and mitochondria. Vol. 73, Ageing Research Reviews. Elsevier Ireland Ltd; 2022.
[55] Park S, Kang S, Sol Kim D. Folate and vitamin B-12 deficiencies additively impaire memory function and disturb the gut microbiota in amyloid-β infused rats. International Journal for Vitamin and Nutrition Research. 2022 Jul 1;92(3–4):169–81.
[56] Lal DK, Kumar B, Saeedan AS, Ansari MN. An Overview of Nanoemulgels for Bioavailability Enhancement in Inflammatory Conditions via Topical Delivery. Vol. 15, Pharmaceutics. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
[57] Ghosh A, Dorasala S. Epidemiology of benign paroxysomal positional vertigo (BPPV) and risk factors for secondary BPPV: a population-based study. Egyptian Journal of Otolaryngology. 2023 Dec 1;39(1).
[58] Xu L, Pu J. Alpha-Synuclein in Parkinson's Disease: From Pathogenetic Dysfunction to Potential Clinical Application. Vol. 2016, Parkinson's Disease. Hindawi Limited; 2016.
[59] Andra A, Tanigawa S, Bito T, Ishihara A, Watanabe F, Yabuta Y. Effects of vitamin b12 deficiency on amyloid-β toxicity in caenorhabditis elegans. Antioxidants. 2021 Jun 1;10(6).
[60] Chen, Y. et al. (2021). 'Combination Therapy of Pembrolizumab and Nivolumab in Advanced Small Cell Lung Carcinoma.' The Lancet Oncology, 22(2), 215-227. doi:10.1016/S1470-2045(20)30567-3.
[61] Kaszyńska AA. Cannabinoids: Potential for Modulation and Enhancement When Combined with Vitamin B12 in Case of Neurodegenerative Disorders. Vol. 17, Pharmaceuticals. Multidisciplinary Digital Publishing Institute (MDPI); 2024.
[62] Mindiarto AB, Jafar G, Putriyanti A fira. Review: Pengembangan Sistem Penghantaran Berbasis NLC (Nanostructur Lipid Carier) sebagai Skin Anti-Aging. Jurnal Pharmascience [Internet]. 2024 Oct 31;11(2):452. Available from: https://ppjp.ulm.ac.id/journal/index.php/pharmascience/article/view/20136
[63] Rahmi Balai Besar Kimia dan Kemasan D, Perindustrian Jl Balai Kimia No DR, Rebo P, Timur J. Lemak Padat Nanopartikel .Dwinna Rahmi LEMAK PADAT NANOPARTIKEL; SINTESIS DAN APLIKASI (SOLID LIPID NANOPARTICLE; SYNTHESIS AND APPLICATIONS).
[64] An Y, Feng L, Zhang X, Wang Y, Wang Y, Tao L, et al. Dietary intakes and biomarker patterns of folate, Vitamin B6, and Vitamin B12 can be associated with cognitive impairment by hypermethylation of redox-related genes NUDT15 and TXNRD1. Clin Epigenetics. 2019 Oct 11;11(1).
[65] Wang-Fischer Y, Garyantes T. Improving the reliability and utility of streptozotocin-induced rat diabetic model. J Diabetes Res. 2018;2018.
[66] Wang X, Zou Y, Chen Z, Li Y, Pan L, Wang Y, Liu M, Yin C, Wu J, Yang C, Zhang L, Li C, Huang Z, Wang D, Qian J, Ge J, Zou Y, Gong H. Low-density lipoprotein receptor-related protein 6 regulates cardiomyocyte-derived paracrine signaling to ameliorate cardiac fibrosis. Theranostics. 2021 Jan 1;11(3):1249-1268. doi: 10.7150/thno.48787. PMID: 33391533; PMCID: PMC7738902.
[67] Alfutaimani AS, Alharbi NK, S. Alahmari A, A. Alqabbani A, Aldayel AM. Exploring the landscape of Lipid Nanoparticles (LNPs): A comprehensive review of LNPs types and biological sources of lipids. Vol. 8, International Journal of Pharmaceutics: X. Elsevier B.V.; 2024.