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RECENT ADVANCES IN NUTRITION TO CONTROL ALZHEIMER'S DISEASE

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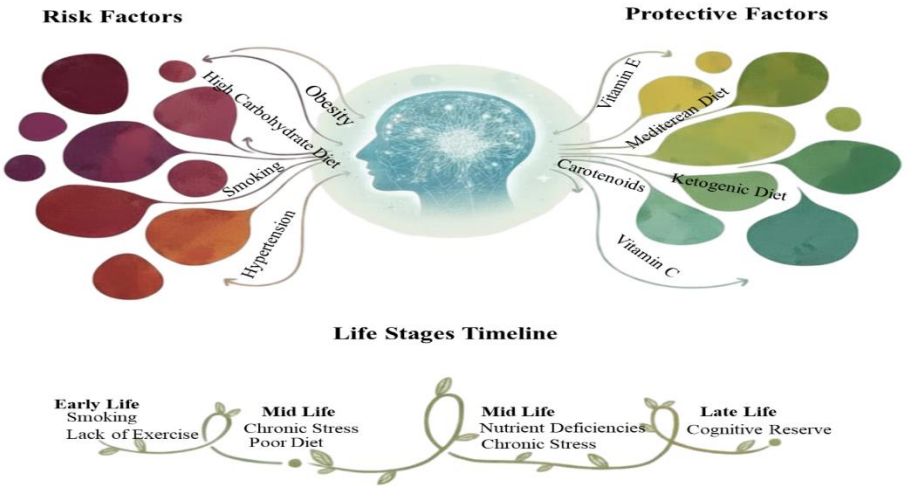
Abstract

Alzheimer's disease AD is a degenerative neurological condition that gradually diminishes cognitive function. Due to the accumulation of beta amyloid peptide (Aβ) and hyperphosphorylated tau protein in the brain, the induction of neuroinflammation through the innate immune responses within the central nervous system CNS is a key contributor to the development of Alzheimer's disease. This review aimed to explore the association between nutrition and Alzheimer's disease (AD) as well as the role of antioxidants in combating the Alzheimer's disease. Second-hand articles obtained from Google Scholar, PubMed, and Scihub were studied. Certain lifestyle risk factors, such as a sedentary lifestyle, unhealthy diet, smoking, hypertension, obesity, and excessive alcohol consumption, may contribute to the onset of AD. The conclusion was that antioxidants have shown promise in combating oxidative stress and protecting cells. Diets including Mediterranean diet (MeDi), have been associated with a reduced risk of developing dementia and improved overall health. Moreover, the ketogenic showing potential benefits in terms of improved cognition, brain metabolism, and AD biomarkers. Overall, these findings highlight the significance of nutrition and antioxidants in managing AD and underscore the importance of adopting healthy lifestyle choices to reduce the risk of developing the condition.



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INTRODUCTION

Alzheimer disease (AD) is one of the greatest medical care challenges of our century and is the main cause of dementia. In total, 40 million people are estimated to suffer from dementia throughout the world, and this number is supposed to become twice as much every 20 years, until approximately 2050 [1, 2].

Alzheimer's disease is a fatal cognitive disorder with proteinaceous brain deposits neuro-inflammation, cerebrovascular dysfunction and ample neuronal loss over time. There are two proteins in the brain that are extensively involved, one is beta amyloid usually just called amyloid, which reaches abnormal levels in the brain of someone with Alzheimer's in the form of senile plaques (SPs) that collect between neurons and disrupts cell functions. Senile plaques constitute the primary hallmark of Alzheimer's disease[3]. Apolipoprotein E (ApoE), one of the major lipid carriers in the brain, is the strongest genetic risk factors for late-onset of AD [4]. However some of its form such as APOE4 performs the task ineffectively. As a result, excessive amyloid accumulates in the brain. The amyloid mechanism that reduce neural connection in the brain and leads to death of neurons[5]. The other protein is called tau, which is hyperphosphorylated tau protein accumulates in form of neurofibrillary tangles (NFTs) inside neurons which impairs the neurons transport system. These tangles can lead to the death of neurons and contribute to the progression of neurodegenerative disease (NDDs) [6]. The physiological structure of the brain and neurons in **(a)** healthy brain and **(b)** Alzheimer's disease (AD) brain source is represented in Figure 1.

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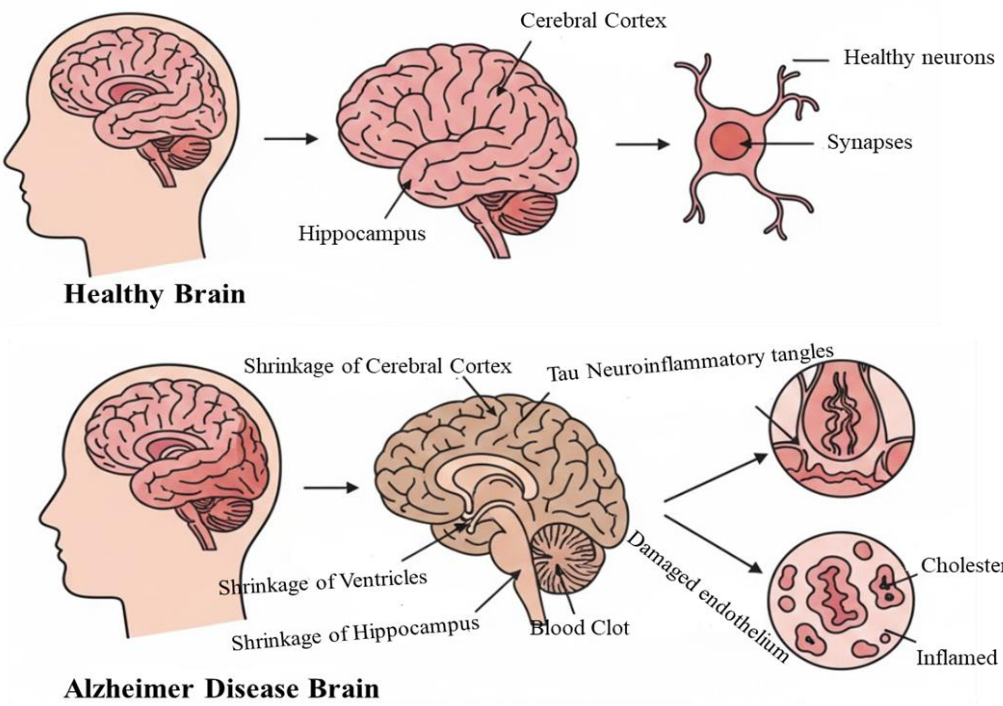

Figure 1. The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

First described in 1906 by Dr. Alois Alzheimer, AD is the most common form of dementia, Approximately 55 million people are living with dementia around world (one new case every 7 seconds) out of this 5.8 million people are living with Alzheimer's disease (AD The World Alzheimer Report 2019 states that this number will escalate rapidly to 88 million by 2050 [7]. Alzheimer's disease (AD) is currently the sixth-leading cause of death in the U.S. The number is projected to be tripled by 2050 due to the aging population, which will increase the risk of burden of illness and health care cost. There is a shortage of healthcare professionals specializing in geriatrics, neurology, and psychiatry to cater to the needs of this population [8 9 10 11].

AD is a progressive neurodegenerative disease that leads to the irreversible loss of neurons and intellectual abilities and eventually causes death within a few years. Currently there are no medical interventions capable of curing or delaying the progression of AD in patients [7].

The number of patients with dementia in China is estimated to be 10–11 million individuals aged 60 years and older or 9–10 million patients aged 65 years and older; 13, 26, 57 more than 60% of patients with dementia have Alzheimer's disease, and approximately 70–80% of them have not received treatment. Not receiving treatment is a substantial problem that occurs because of economic difficulties and low awareness of this disease among patients and their families[12].

Research has strengthened the idea that age is a key factor for AD, it is classified into early stage

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(mild), middle stage (moderate), and late stage (severe forms). Mild and moderate stages may last for years at a time as the individual's memory, cognitive ability, and ability to live independently slowly declines [13]. The underlying disease process of AD is not yet fully understood [14]. No effective pharmacological is currently available to cure AD. Preventive strategies and nutritional intervention seems to be promising strategies to delay neuro cognitive decline and reduce or even prevent the risk of AD. Nutrition has multiple effects on nerve cells functions and thus, leads to the development of many diseases like AD [15]. A healthy diet must be considered, as it offers both protective and preventative benefits against AD. Healthy diet patterns for AD are characterized by high intake of plant-based foods, caffeine, isoflavones, phytoestrogens, polyphenols, minerals (while avoiding copper, iron, and aluminum), probiotic, vitamin B, vitamin D, antioxidants vitamins (such as vitamin C and E, beta-carotene), soy beans, nuts and omega-3 polyunsaturated fatty acid. Moreover low intake of saturated fats, animals- derived proteins and refined sugars, have been revealed to decrease the risk of neuro cognitive impairments and ultimately the onset of AD [16].

The characteristic symptoms of AD are difficulties with memory, language, problem-solving and other cognitive skills that affect a person's ability to perform everyday activities. These difficulties occur because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged or destroyed[17, 18].

Alzheimer's disease (AD) is also associated with eating disorders, including appetite changes, and more than 80 percent of elderly patients with AD experience difficulties in eating and swallowing. There is a correlation between the decline in nutritional status and a rapid decline in cognition, increased institutionalization, and reduced mobility [19].

Methodology

This study was mainly based on the articles from Google scholar, PubMed, Scihub. Research studies from 2019 to 2023 were used for this review. Most of the listed references were within the last 5 years. About 800 articles were downloaded for this study and nearly 139 articles were selected based on inclusion criterion paper having role of nutrients in causing or preventing memory loss. Remaining articles were excluded based on exclusion criterion because they were misappropriating to this topic. In this study main focus is on nutrition and that how nutrition affects brain. Certain lifestyle risk factors i.e. cigarette smoking, obesity and hypertension that negatively affect brain. Antioxidants, including Vitamin E, C, Carotenoids and polyphenols were also discuss in this study, which plays a vital role in brain health. Diet therapy was also included in this review like Mediterranean diet and Ketogenic diet to prevent and control risk of dementia.

Lifestyle risk factors of Alzheimer's disease

Alzheimer's disease has had a tremendous impact on affected individuals, caregivers, and society. However, increasing evidence strongly suggests potential risk factors and roles of vascular disorders and risk factors (such as cigarette smoking, midlife high blood pressure, obesity, diabetes, cerebrovascular lesions), as well as the possible beneficial effects of psychosocial factors (such as

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higher education, active social engagement, physical exercise, and mentally stimulating activities) in the pathogenesis and clinical manifestation of AD [20].

Nonadjustable risk factors for AD include family history, aging and head injury. Epidemiological evidence suggests that up to 3 million AD cases worldwide could be prevented with a 10%-25% in known modifiable midlife risk factors (Cognitive engagement, diet/nutritional supplement intake, physical activity level, type 2 diabetes, alcohol consumption level, mood disorders, hypertension, hypercholesterolemia, and smoking[21] [22].

Cigarette smoking

Approximately 1 billion individuals worldwide utilize tobacco products in the form of cigarettes, and there are at least 6 million global deaths caused annually by diseases related to tobacco smoking [23]. Epidemiological studies have shown that cigarette smoking is an important risk factor of cognitive decline and AD, the most common form of dementia. It is now apparent that smoking-related morbidities are increasing day by day and include neurobiological and neurocognitive abnormalities (e.g., hippocampal volume loss, learning and memory deficits) that are not solely attributable to the foregoing medical conditions and some abnormalities show significant progression over time. Importantly, some of these smoking-related neurobiological abnormalities may represent risk factors for Alzheimer's disease (AD). Correspondingly, there is now substantial epidemiologic evidence from meta-analyses and cohort-based studies that indicates smoking is associated with a significantly increased risk for AD neuropathology and associated dementia,[10]

Cigarette smoking not just doubles the risk of developing dementia and AD; it also accelerates the rate of cognitive decline in elderly without dementia. Apart from active smoking, recent study shows that exposure to secondhand smoke i.e. passive smoking can also increase the odds of developing cognitive impairment. Subjects who have been exposed to secondhand smoke for more than 25 years and have history of carotid artery stenosis have a 3-fold increased risk for dementia. Although these studies suggest a linkage between cigarette smoking (both active and passive) and cognitive impairment, there is insufficient experimental data demonstrating how smoking induces cognition-related pathological changes [24].

In a study supported by the tobacco industry, cross-sectional studies consistently observed that smoking increased the risk for AD and cognitive decline. The increased risk was found in both APOE 4 allele carriers and non-carriers. Particularly, midlife smoking was associated with an increased risk of AD [23]. According to a study, early-life exposure to secondhand smoke was significantly associated with an increased risk of dementia [25]. Smoking is linked to cognitive impairments and decline, as evidenced by faster declines in verbal memory and slower visual search speed [26]. Several large population-based cohorts have reported a 2-4 fold increased risk of being diagnosed with AD among current smokers, but only in APOE4 non-carriers. A more recent meta-analysis of 37 prospective cohorts has confirmed that smoking increases the risk of all dementia and vascular dementia [27].

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The possible mechanism through which smoking affects is as follows: Cerebral blood flow is mainly regulated by nitrergic nerves and nitric oxide (NO) liberated from endothelial cells in response to shear stress. Endothelium-derived NO and nitrergic nerves play some roles as vasodilator factors. Cigarette smoking impairs NO synthesis in cerebral vascular endothelial cells and nitrergic nerves leading to interfere with cerebral blood flow and glucose metabolism in the brain. Smoking-induced cerebral hypo perfusion is induced by impairment of synthesis and actions of NO and by increased production of oxygen radicals, resulting in decreased actions of NO on vascular smooth muscle. Nicotine acutely and chronically impairs the action of endothelial NO. Impaired cerebral blood supply promotes the synthesis of amyloid β that accelerates blood flow decrease. This vicious cycle is thought to be one of the important factors involving in Alzheimer's disease (AD). Quitting smoking is undoubtedly one of the important ways to prevent and delay the genesis or slow the progress of impaired cognitive function and AD [28] . Summarized scheme of direct and indirect actions of smoking on NO synthesis, action and degradation, cerebral blood flow, and Aβ synthesis/degradation in the pathogenesis of AD is represented in Figure 2.

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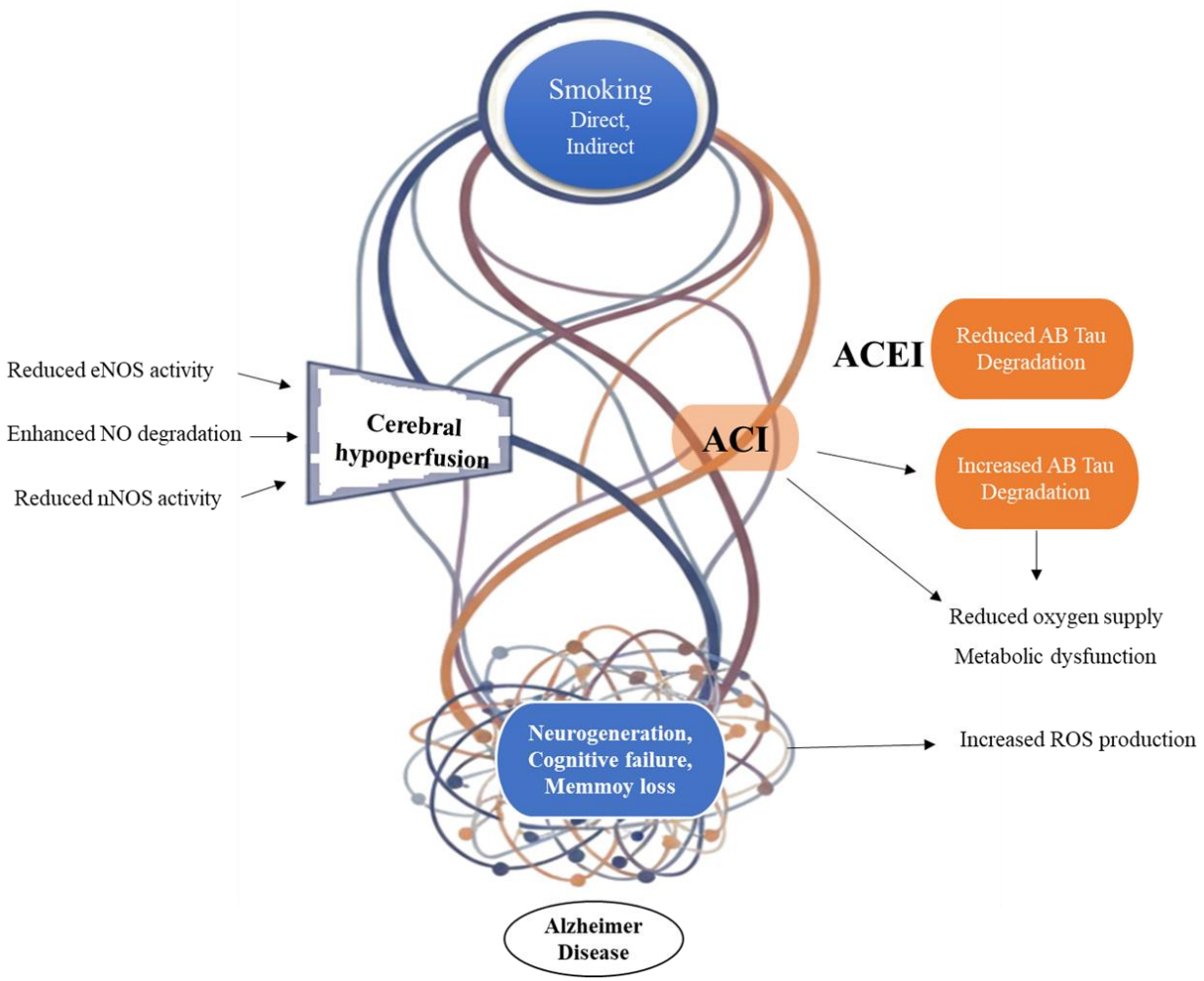

Fig. 2. Summarized scheme of direct and indirect actions of smoking on Nitrogen Oxide synthesis, action and degradation, cerebral blood flow, and Aβ synthesis/degradation in the pathogenesis of AD. ACEI: angiotensin converting enzyme inhibitor.

Obesity

Nutrition plays a crucial role in both the prevention of dementia and the management of nutritional challenges arising from dementia[29]. Increasing evidence suggests that abnormal cerebral glucose metabolism is predominantly present in Alzheimer's disease (AD). It is described that numerous interrelationships between abnormal glucose metabolism and the occurrence of brain lesions exist [30].

The brain relies on glucose as its primary energy source, and a decline in its metabolism directly affects brain function. Clinical reports indicate progressive neuro-degeneration accompanied by a

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gradual loss of cognition and memory, all of which are symptoms of Alzheimer's disease (AD) [31].

For a long time, the association between obesity and cognitive impairments went unexplored. Nowadays, increasing epidemiological data supported an important relationship between these conditions. Various factors could be implicated in the development of AD in obese individuals, such as increased levels of apolipoprotein in adipose tissue and Aβ in plasma [32]. Metabolic changes caused by overweight are related to damage to the central nervous system (CNS), which can lead to neuronal death, either through apoptosis or cell necrosis, as well as alter the synaptic plasticity of neurons[33]. There is indication that obesity accelerates memory dysfunction and neuroinflammation in AD. The overweight in the elderly of 70 to 88 years and older has also been notified as a risk factor for AD [34].

Epidemiological studies have demonstrated that individuals with obesity and diabetes have a fourfold increased risk for Alzheimer's disease (AD). The health risks linked to obesity, including evidence suggesting that obesity may causally promote the degenerative process of AD, are of significant concern for public health [35].

Moreover, recent findings of a link between obesity and AD should be interpreted with caution. This is because metabolic abnormalities, like high blood sugar levels and abnormal levels of fats in the blood, often coexist with obesity and may distort the true impact of obesity on the risk of AD [36] [37].

A recent meta-analysis showed that blood concentrations of several inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin (IL) 6, and IL-1β are increased in AD patients. Overproduction of pro-inflammatory cytokines, including TNF-α is a key feature of the pathophysiology of metabolic disorders. TNF-α is over expressed in adipose tissue of obese individuals. Studies by Hotamisligil and colleagues, demonstrated that elevated TNF-α levels cause peripheral insulin resistance. Interestingly, brain inflammation has recently been proposed to underlie defective neuronal insulin signaling in AD. Several pathological features, including impaired insulin signaling and inflammation, appear to be shared by patients with diabetes and patients with AD. Therefore, it is likely that mechanisms analogous to those that account for peripheral insulin resistance in type 2 diabetes underlie impaired brain insulin signaling and neuronal dysfunction in AD. Molecular/cellular mechanisms underlying defective brain insulin signaling and neuronal dysfunction in AD is an evidence that AD and diabetes share common inflammatory signaling pathways [38]. Figure 4. The impact of metabolic disease (T2D and obesity), mitochondrial dysregulation, and the generation of pro-inflammatory cytokines that cross the blood–brain barrier, inducing a cycle of neuroinflammation and increasing the rate of Aβ-plaque generation. Aβ peptides drive the development of ROS, mitochondrial dysfunction, and pro-inflammatory cytokines, which serves to increase AD pathology cyclically, is represented in Figure 3.

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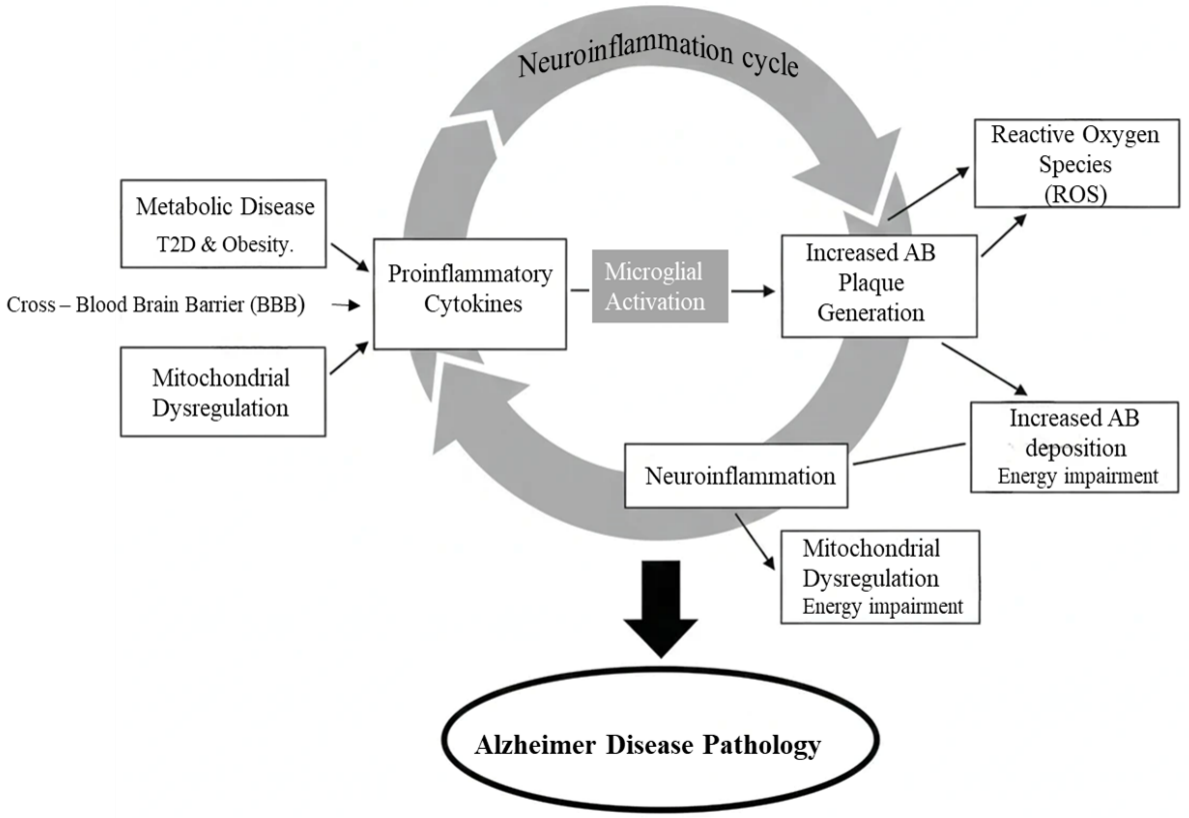

Figure 3. The impact of metabolic disease (T2D and obesity), mitochondrial dysregulation, and the generation of pro-inflammatory cytokines that cross the blood–brain barrier, inducing a cycle of neuroinflammation and increasing the rate of Aβ-plaque generation. Aβ peptides drive the development of ROS, mitochondrial dysfunction, and pro-inflammatory cytokines, which serves to increase AD pathology cyclically,

Ultra processed food (UPF) consumption is associated with obesity, cardiovascular diseases, dementia and AD. During a study by Li et al., 2022 about seven thousand participants 518 patients developed dementia of whom 287 developed Alzheimer disease Higher consumption of UPF was associated with higher risk of dementia, whereas substituting unprocessed or minimally processed foods for UPF was associated with lower risk of dementia

Hypertension

Resent study have demonstrated that older people who have high blood pressure (BP), or

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hypertension, are more likely to have biomarker of Alzheimer's disease (AD). High BP can damage small blood vessels in the brain, impacting those parts that are responsible for memory and thinking [39]. Midlife (45–65 years) hypertension is a known contributor to the etiology of late-life (older than 65 years) dementia and is increasingly involved as a risk factor for the development of AD. For example, a recent epidemiological study found that midlife stage 1 (systolic blood pressure > 140 mmHg) and stage 2 (systolic blood pressure > 160 mmHg) hypertension increases the risk of AD by 18% and 25%, respectively. Animal studies have demonstrated that chronically elevated blood pressure leads to adverse glial activation and increased brain inflammatory mediators [40] Hypertension is among the risk factors for AD that have been associated with underlying pathological changes such as the formation of senile plaques and neurofibrillary tangles as well as hippocampal atrophy [41].

Human imaging and autopsy studies indicate that midlife and late life hypertension is associated with increased AD pathological change. Emerging research has suggested that instead of the average blood pressure (BP), it is the negative BP patterns or the fluctuation in BP contributes to AD [42]. Observational studies suggest the association between high BP and late-life dementia is strongest when BP levels are measured in mid-life [43]. Vascular risk factors associated with AD, such as hypertension and atherosclerosis, cause additional damage leading to progressive cerebral hypopurfusion [44]. Hypertension is common in AD patients, and it has been suggested that it plays a critical role in the progression of the disease. For example, a recent Swedish study demonstrated that 37% of AD patients examined had clinically manifested hypertension [20].

Hypertension can also lead to changes in the white matter of the brain and is linked to the unusual buildup of Aβ, which are common characteristics of AD [45]. Hypertension is capable of causing changes in the vascular walls which can lead to hypoperfusion, ischemia and cerebral hypoxia, related to trigger the development of AD [46]. Experimental studies have demonstrated that a high level of cholesterol in the diet increase the chance of developing Alzheimer's disease [47] [27, 48]

Cerebrovascular changes such as hemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies and white matter changes increase the risk of dementia but the specific underlying mechanism remain unclear. Infarcts or white matter hyperintensies may lead directly to the damage of brain regions that are important in memory function, such as the thalamus and the thalamo-cortical projections. However, they may also increase the deposition of Aβ, which in turn can lead to cognitive decline (Christiane and Mayeux 2014). Epidemiological studies have proven that cardiovascular risk factors are associated with cognitive decline and that their modification might prevent or delay the progression of at least 40% dementia worldwide [49]. Cerebro-microvascular alterations by which hypertension promotes the pathogenesis of vascular cognitive impairment and AD is represented in figure 4.

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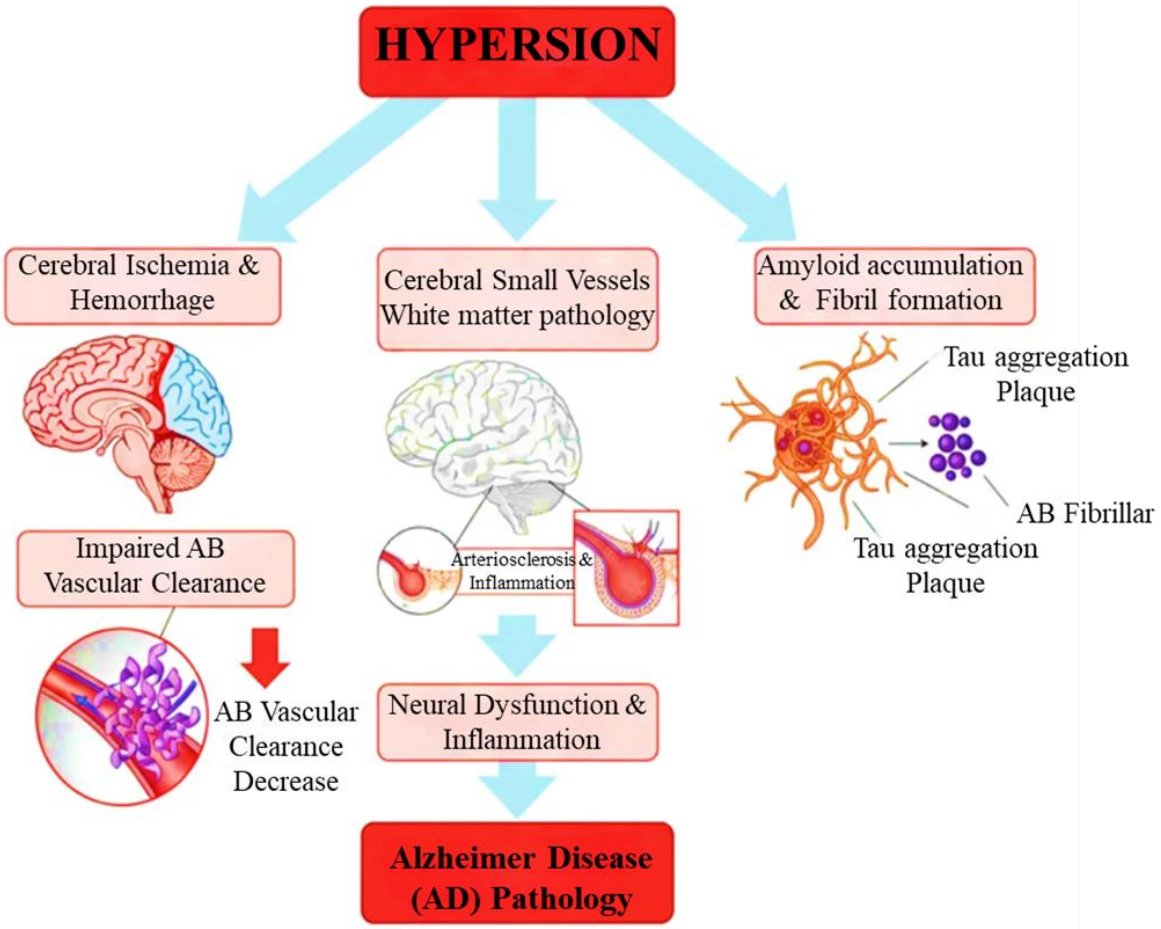

Figure 4. A detailed description of the pathophysiological association between Alzheimer's Disease and hypertension.

Role of antioxidants rich diet in Alzheimer's disease

It is well established that diet affects both mental and physical health. Food sources have significant role in treating AD, as reported in many studies. [50] observed that AD may necessitate the normalizing of extracellular and intracellular PH with simultaneous supplementation of an antioxidant combination at a sufficiently high dosage [11].Vitamin E, C, carotenoids, flavonoids, polyphenols (Table 1) and are natural dietary antioxidants used as a medicine for the treatment of AD [51]. Influence of bioactive compounds on the pathogenesis of Alzheimer's disease. Reduction of

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Aβ levels and tau phosphorylation rate. Prevention of Aβ and tau aggregation, defense against oxidative stress, anti-inflammatory activity, protection of cellular structures and inhibition of neuronal apoptosis represented in figure 5.

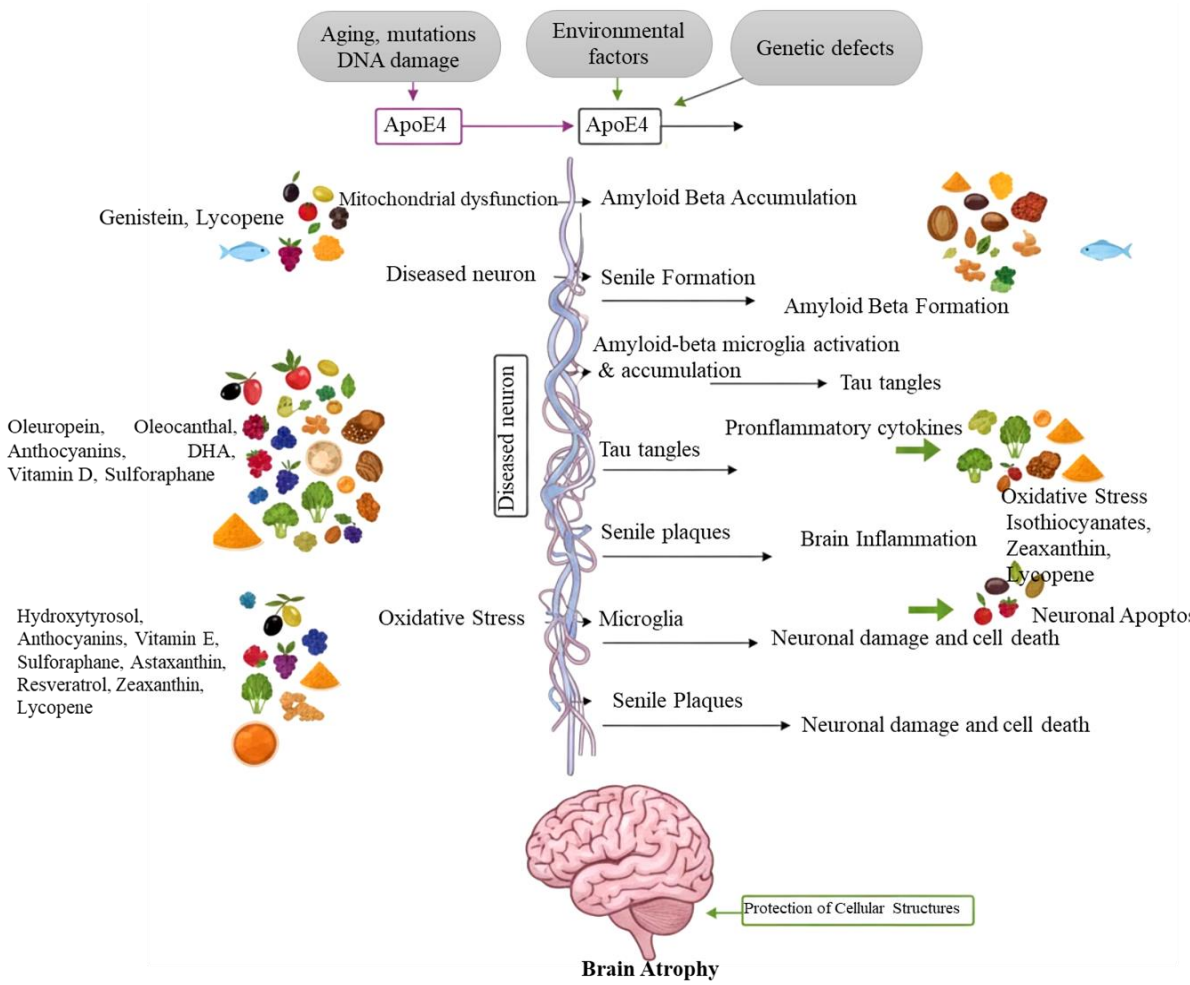

Figure 5. Influence of bioactive compounds on the pathogenesis of Alzheimer's disease. Reduction of Aβ levels and tau phosphorylation rate. Prevention of Aβ and tau aggregation, defense against oxidative stress, anti-inflammatory activity, protection of cellular structures and inhibition of neuronal apoptosis.

Vitamin E

Vitamin E is frequently linked with health benefits, such as antioxidant, anti-inflammatory and cholesterol-lowering and anti-cancer effects. Vitamin E is also important for the central nervous system and its role in prevention and treatment of some neurological disease has been suggested [52].

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These qualities make it a potential therapy for neurodegenerative condition, for example, Alzheimer's or Parkinson's disease[53]. As oxidative stress plays a main role in AD, Administration of antioxidants like Vitamin E is suggested. Indeed, many case-control studies proved the association between increasing oxidative stress in AD and reduction of Vitamin E level [54]. Mullan and colleagues conducted a recent meta-analysis in 2018 that included 51 studies comparing the plasma nutrient status of people with Alzheimer's disease to those without cognitive impairment. The study found that vitamin E was the most commonly studied dietary plasma antioxidant. Their conclusion was that people with Alzheimer's disease have 11% lower vitamin E levels than those without cognitive impairment [55].

Vitamin E has been reported to other biological effects. For example, vitamin E can activate PP2A, a phosphate that plays an essential role in tau protein homeostasis and has been proved to be downregulated in the brain of AD patients[52, 56]. Amyloid β accumulation in AD increases free radical formation, and also indirectly causes the formation of pro-oxidants by stimulating inflammatory cells. It is thought that vitamin E may contribute to protection against lipid peroxidation in the brain thanks to it antioxidant activity[57].

Vitamin E is a potent antioxidant that helps to protect cells from harmful free radicals. The research conducted by Dysken in 2014 is compelling and suggests that vitamin E may help to slow the decline of cognitive function in Alzheimer's disease [38]. A daily recommended intake of vitamin E in Poland is 6 mg for kids, 10 mg for men, 8 mg for women and 20-25 mg for older people (above 75 years old). Vitamin E exhibits the most powerful antioxidant properties resulting in its capacity to eliminate excessive amount of free radicals in human cells and stop peroxidation of lipids. All these neuroprotective processes prevent cells from hemolysis and their premature death [58].

Vitamin E has been linked to neurogenesis, neural differentiation, synaptic function in the hippocampus, and cell signaling pathways. As a result, it plays a neuroprotective role in the brain [59].

Vitamin E is found in vegetable oils and products obtained from vegetables, whole grains, nuts and seeds, animals fats and meats, with variations in levels of tocopherols between food sources for example while some oils such as soybean oil, contain a mix of tocopherols [60].

Vitamin C

Ascorbic acid is sold as a dietary supplement and is used daily by millions of people worldwide [61]. It is water – soluble vitamin, highly concentrated in the brain and participates in neuronal modulation and regulation of central nervous system (CNS). Ascorbic acid has been found to have a neuroprotective effect against neurodegenerative diseases, such as Alzheimer's disease [62]. Research shows that normal vitamin C intake has neuroprotective effects and may help improve cognition in AD patients [63].

Vitamin C has antioxidant effects and improves cognitive functions in patients with Alzheimer's disease [64]. The deficiency of vitamins in the body causes neurological disorder like Alzheimer's disease. Vitamin C deficiency causes demyelination of neurons. A lack of vitamin C reduces antioxidant levels, increases oxidative stress, and disrupts the glucose cycle [65]. Brain function can

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also be influenced by vitamin C deficiency, since collagen type IV (a protein dependent of ascorbic acid for synthesis) is crucial for myelin structure and brain electric activity[66].

A literature review from 2012 that evaluated the impact of ascorbic acid on cognitive functions found mixed results on the effectiveness of vitamin C use in Alzheimer's disease. The hypothesis was that the brain uses ascorbic acid from the peripheral pool to endure oxidative stress. [67].

Recently, some lines of evidence implicated that vitamin C exerted anti-inflammation activity. For example in a colchicine induced neuroinflammation AD rat model, supplement of vitamin C lowered memory impairment and inflammatory markers such as tumor necrosis factor and interleukin 1 beta in the hippocampus of AD rats[68]. Vitamin C can be found in many natural sources, particularly fresh fruits and vegetables. The richest sources of ascorbic acid including Indian gooseberry, citrus fruits such as limes, oranges and lemons, tomatoes, papaya, green and red peppers, kiwifruit, strawberries and cantaloupe[69].

Carotenoids

Carotenoids are plant pigments responsible for bright red, yellow and orange hues in many fruits and vegetables that exhibit strong antioxidant properties. Recent epidemiological studies indicate that consuming foods rich in carotenoids can lower the risk of certain diseases, including neurodegenerative diseases. Carotenoids exert brain and cognitive protection that can help prevent the onset and progression of Alzheimer's Disease [70].

Oxidative damage refers to tissue injury due to cumulative exposure to unstable molecules known as reactive oxygen species (ROS). Examples of ROS include free radicals, singlet oxygen, and hydrogen peroxide. Carotenoids with a higher number of conjugated double bonds have a greater capacity to scavenge ROS and thus are more powerful antioxidants [71].

Lutein is the primary carotenoid found in human brain tissue, particularly in areas that regulate various cognitive functions. Out of all carotenoids, only lutein has consistently been linked to a broad range of cognitive processes, including language, learning, memory, and executive function [72].

Dietary intake of lycopene improved cognitive function in a tau transgenic mouse model of AD. A higher level of lutein in relation to plasma lipids was observed to lower the risk of Alzheimer's disease [73] higher intake of total carotenoids or lutein/zeaxanthin over more than a decade was linked with almost 50% lower risk for an AD diagnosis and less global brain pathology[74].

One of the most beneficial carotenoid compounds is astaxanthin. It acts as a free radical scavenger and reduces oxidative stress, lipid peroxidation, and protein peroxidation products[75]. B-carotene is a carotenoid responsible for the red and orange pigments found in certain fruits and vegetables, such as carrots, sweet potatoes, and squash. It can protect against oxidative stress and may have a beneficial effect on neuronal development [76] Several diseases are due to Ca2+ inability to signal the molecules but carotenoids like astaxanthin, β-carotene and lycopene are involved in Ca2+ ion transportation in brain, with proper dietary intake of carotenoids improper signaling can be reduced [76] conducted a study that examined the concentrations of carotenoids, alpha tocopherol, lutein and retinol in the brain tissue. The study found that lutein was consistently linked to better performance

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on global and domain-specific measures, including executive function, language, learning, and memory [77]

The data from 2011–2014 National Health and Nutrition Examination Survey involving 2796 participants aged ≥60 years demonstrated that lutein and zeaxanthin supplementation (2.02 mg/day) may prevent cognitive decline (Tan et al., 2019). Recent studies using animal models have demonstrated that lycopene can protect the brain by reducing oxidative stress, suppressing the production of inflammatory cytokines, and decreasing the accumulation of amyloid plaques [78].

Saffron is a plant material obtained from *Crocus sativus*. It is a substance rich in carotenoids (crocin, crocetin), monoterpene aldehydes, and flavonoids. Research has shown that saffron affects the functioning of the nervous system [58].

Polyphenols

Polyphenols are naturally occurring substances present in plants, fruits and vegetables and are known to have neuroprotective effects. There are many important dietary sources of polyphenols, including fruits (apple, barriers, cocoa, vegetables, herbs, grains, red wine, nuts, tea, onions, and seeds). Studies have shown that dietary polyphenols can help prevent the development of Alzheimer's disease. This is because they can cross the blood-brain barrier [58]. First investigation on polyphenols antioxidant activity is dated almost twenty years ago with their relationship and implications with the prevention and treatment of cancer was proposed for the first time. Later in the early 2000, the neuro protective were demonstrated [79].

The most common group of polyphenolic compounds is represented by flavonoids and the main subclasses flavanols, flavones, flavanones, flavan-3-ols, anthocyanins, and isoflavones, largely contained in fruits and vegetables [80]. Flavonoids are known to have neuroprotective properties due to their polyphenolic composition. They can act as antioxidants by scavenging free radicals like superoxide radicals and hydrogen peroxide. The number and location of hydroxyl groups in polyphenols can affect their ability to scavenge free radicals [81].

A study investigated the association between dietary polyphenols and sleep quality in 92 normal-weight and obese young women, reporting that only higher polyphenol were inversely associated with poor sleep quality and mental health[82]. Curcumin is another polyphenol that showed promised results in preclinical studies[83]. Studies have reported that curcumin can bind to metal ions, which helps prevent them from causing the aggregation of AD, and it can also reduce oxidative stress[51]. Furthermore, the ability of polyphenols to lower the cholesterol levels in cells. Apart from the anti-amyloid functions, polyphenols also possess the ability to inhibit tau aggregation [84].

Flavonoids have been found to have many neuroprotective effects that can help prevent neurodegenerative diseases. They can reduce neuroinflammation and improve cognitive function. A recent study found that a flavonoid extracted from the caper leaf and fruit has anti-amyloid properties[85].

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Omega-3 Fatty acid

Aβ is removed from the brain through various clearance routes, including enzymatic degradation, autophagy-mediated degradation, cellular uptake, glymphatic system and transport across the blood–brain barrier (BBB)[86]. Each route contributes to the Aβ clearance, but BBB transport predominates all other routes. A number of studies have documented that the BBB clears the majority of extracellular Aβ (75%) by a number of specialized transport proteins. Low-density lipoprotein receptor-related protein 1 (LRP-1) is one such transport protein, and binds to multiple ligands modulating the outflow of toxin Aβ. The impairment of LRP-1 contributes to Aβ aggregation and deposition in the brain [87]. Dietary supplementation with fish oils or relatively pure ω-3 polyunsaturated fatty acids (ω-3 PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), as well as ω-6 polyunsaturated fatty acids (ω-6 PUFAs) like arachidonic acid (AA) exerts protective roles in reducing Aβ accumulation [88]. DHA is highly concentrated in the brain and plays an essential role in brain functioning. DHA, readily crosses the blood–brain barrier from blood to the brain. Its critical role was further supported by its reduced levels in the brain of Alzheimer's disease (AD) patients [43]. Since there is yet no cure for dementia such as AD, there is growing interest in the role of DHA-supplemented diet in the prevention of AD pathogenesis. Accordingly, animal, epidemiological, preclinical and clinical studies indicated that DHA has neuroprotective effects in a number of neurodegenerative conditions including AD. The beneficial effects of this key omega-3 fatty acid supplementation may depend on the stage of disease progression, other dietary mediators and the apolipoprotein ApoE genotype [89].

Gut Microbiome and AD

There is proof that nutrition and the gut microbiota may play a role in the onset or prevention of AD. Immune cells in the mucosa, endocrine cells, or the vagus nerve can transmit information between the brain and the intestine. The process of aging is linked to intestinal dysbiosis, which is typified by a decrease in anti-inflammatory response-mediating bacteria and an increase in pro-inflammatory pathogenic bacteria. This dysbiosis ultimately causes neuroinflammation and neuronal damage, which in turn causes cognitive loss [90]. Thus, neurodegenerative illnesses are significantly impacted by the microbiota–gut–brain axis [91].

There is evidence to suggest that GM contributes to the pathogenesis and progression of AD; it may do so by functioning as a preventive measure, reducing the symptoms of the condition, or serving as a causative factor[92] [92]. It is made up of a wide community of microorganisms that can affect brain processes by the release of biologically active compounds and afferent signaling pathways. These microorganisms include bacteria, fungi, viruses, and archaea[93]. This intricate web of microbes is essential for both the development of the immune system and the digestion and absorption of nutrients. According to [94], bacteria are essential for the fermentation of indigestible carbohydrates, the synthesis of vitamins, and defense against pathogenic invaders.

Studies showed that the aging process is associated with an imbalance among GM microorganisms, known as intestinal dysbiosis, which is a risk factor for AD through the activation of neuroinflammation and amyloid formation [95] [92]. Furthermore, several lifestyle factors play a crucial

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role in affecting the GM, influencing its composition and balance throughout life. Diet, in turn, has a direct link to intestinal modulation, and fat intake can act as a risk factor or prevent AD by modulating GM composition [96].

Table 1. Nutrients Modulating Alzheimer Disease Pathology

Nutrient	Target Mechanism	Impact on AD	Specific Nutrients	Dietary Sources	Study Type / Population	Outcomes Measured	Dosage / Duration	Limitations / Controversies	Evidence (Author – Year)
Omega-3 fatty acids	Enhance Aβ clearance across BBB; anti-inflammatory signaling; synaptic membrane fluidity	↓ Aβ burden; improved synaptic integrity; cognitive support	DHA, EPA	Fatty fish (salmon, mackerel, sardines), algae oils	RCTs (mild AD, MCI, elderly cohorts); meta-analyses	Cognitive scores, CSF Aβ, synaptic markers	DHA ≥1–2 g/day, multi-month trials	Limited efficacy in advanced AD; APOE4 genotype interactions	[97-99]
Polyphenols	Inhibit Aβ aggregation; modulate tau phosphorylation; antioxidant & anti-inflammatory	↓ Aβ/tau aggregates; neuroprotection; potential cognitive benefit	Curcumin, EGCG, resveratrol, quercetin	Turmeric, green tea, grapes/red wine, onions	RCTs (curcumin in AD); translational animal-human studies; reviews	Biomarkers (Aβ/tau), cognition, oxidative stress	Curcumin 1–4 g/day; EGCG ~300–600 mg/day	Poor bioavailability; inconsistent clinical endpoints	[100, 101]

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Carotenoids	ROS scavenging; membrane stabilization; anti-inflammatory antioxidant	Neuroprotection; improved memory/cognition	Lutein, zeaxanthin, β-carotene	Spinach, kale, corn, egg yolks, carrots	Cohort studies (elderly); intervention trials	Cognitive tests, serum/brain carotenoid levels	Lutein/zeaxanthin 10–20 mg/day	Observational associations; limited causal interventional data	[102-104]
Vitamins (B, C, E)	Reduce oxidative stress & neuroinflammation; B vitamins lower homocysteine	Improved cognition; ↓ neuronal damage in deficiency states	Vitamin E (α-tocopherol), vitamin C (ascorbate), folate, B6, B12	Nuts/seeds (E), citrus (C), leafy greens/legumes (folate), animal products (B12)	RCTs (vitamin E in AD); cohort studies (B vitamins, dementia risk); meta-analyses	Dementia risk, cognitive decline, homocysteine levels	Vitamin E 200–2,000 IU/day; B-vitamin regimens for homocysteine	Mixed RCT results; high-dose E risks; confounding in cohorts	[105, 106]

Diets in Alzheimer's disease

The Mediterranean diet and Dash diet both contain plenty of plant-based products and minimal amount of red meat and processed meat. These diets are thus rich in omega-3 fatty acids, antioxidants and polyphenols which appears to protect brain against AD by reducing oxidative stress and neuro-inflammation [76, 107].

The Mediterranean diet (MedDiet) as a model of healthy eating The Mediterranean Diet is a dietary pattern that involves eating more olive oil, vegetables, fruits, nuts, and legumes. It also includes moderate amounts of fish, meat, dairy products, and red wine [108]. This type of diet has been linked to a lower the risk of non-communicable diseases like cardiovascular diseases, type 2 diabetes, certain cancers, and dementia [109]. The Western diet, which is low in fiber, may be linked to AD. On the

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other hand, the Mediterranean diet (MeDi), which is high in nutrient-dense foods, may not only be beneficial for overall health but also for healthy brain aging. Studies have found that following the MeDi is associated with a lower risk of dementia[110].

A growing body of recent reports has indicated that the MeDi diet has a striking effect in preventing aging related cognitive decline and reducing the risk of AD [20]. Two cohort studies conducted in the Mediterranean region used longitudinal analysis to examine the relationship between adherence to the MeDi diet and the risk or incidence of all-cause dementia. The studies found that higher adherence to the MeDi diet was associated with a lower risk (72% lower) and incidence (20% lower) of all-cause dementia [111].

Scientific evidence demonstrates MD effects on cognition. A recent meta-analysis concluded that high adherence to MD reduced the risk of global cognitive decline in non-demented older adults over 60 years of age[112]. Many of the studies that have assessed the association between MD and dementia risk have taken place in non-Mediterranean countries, mostly the United States. These studies would support the external validity of the beneficial effect of the MD[113] (Andreu-Reinon et al., 2021). Research indicates that adherence to MedDiet during midlife is associated with 36%-46% greater likelihood of healthy aging. Furthermore, MedDiet has a positive impact on hospitalized patients i.e., it slows down their rate of stay length and in-hospital mortality [113].

The popularity of the MeDi diet can be attributed to the Seven Countries Study, which stated that people with high adherence to this diet pattern were at a reduced risk of death [114]. The Mediterranean diet's key ingredients include various bio-active nutrients that may be advantageous for cognitive health. For instance, extra virgin olive oil contains monounsaturated fatty acids, while nuts and fish contain polyunsaturated fatty acids. These fatty acids have anti-inflammatory effects that could enhance cerebral blood vessel functioning [115].

Ketogenic diet

Ketogenic diet (KD) was first introduced by Dr. Russell Wilder in 1921 and is characterized by a high fat, moderate protein, and a low carbohydrate diet [116]. KD has also been reported to reduce neuroinflammotery, which has been proposed to be advantageous for treating neurological disease. Inflammation in the brain was also decreased by KD consumption[117]. Alzheimer's disease is very difficult to prevent and treat using the medicine available today. However, there has been some hope with using a ketogenic diet to reduce the cognitive and quality of life declined experienced by patient with AD [9]. Animal studies have shown that KD reduces the volume of Aβ and tau protein aggregates, and reduces their toxicity. However, this effect is limited to preventing the formation of new plaques [118].

There is evidence to suggest that KD plays neuroprotective and disease modifying role in neurodegenerative disease by regulation both central and peripheral inflammatory mechanism [119]. It was a common phenomenon that energy deprivation in neurological disorders, including Alzheimer's disease, progress rapidly. Ketone bodies have the ability to stabilize mitochondrial energy metabolism making them a suitable intervention agent [120]. The classic KD is characterized by

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a 4:1 ratio of fats to carbohydrates and proteins, where for every 4 g of fats, there is 1 g of carbohydrates and proteins combined. It is generally believed that in a KD about 70%–80% of energy should come from fat, and the rest of the requirement should be covered by proteins and carbohydrates [121].

During the KD, fatty acids are converted to ketone bodies (KBs) by liver metabolism and then enter the bloodstream to induce nutritional ketosis and participate in subsequent physiological or pathological reactions[119]. The ketogenic diet is a method of nutrition that leads to the increased production of ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) in the body, resulting in a condition of ketosis. This is achieved by obtaining the majority of energy from fats and minimizing the intake of carbohydrates[122]. [123] Brain energy metabolism is impaired in AD. Ketogenic diets can theoretically mitigate impaired brain energy metabolism in AD, leading to improved cognition, daily function, or quality of life[123].

Therefore, although several studies have reported the impact of the ketogenic diet on Alzheimer's disease (AD), it appears that the relationship between these two variables (diet and brain disease) is complex and influenced by several factors. As previously mentioned, mood disorders and changes in various neurotransmitters have been observed in patients with AD[124]. A modified Atkins ketogenic diet (Atkins-KD) was proposed in 2003. In Atkins-KD, carbohydrates are restricted, providing 5% energy, while proteins and fats provide approximately 25% and 70%, respectively [125]. Another study demonstrated in a small group of patients that 6 weeks on a KD improved verbal memory performance evaluated with patients on a high carbohydrate diet[126]. Figure 6. Potential mechanisms of the ketogenic diet effect in neurological diseases are represented in figure 6.

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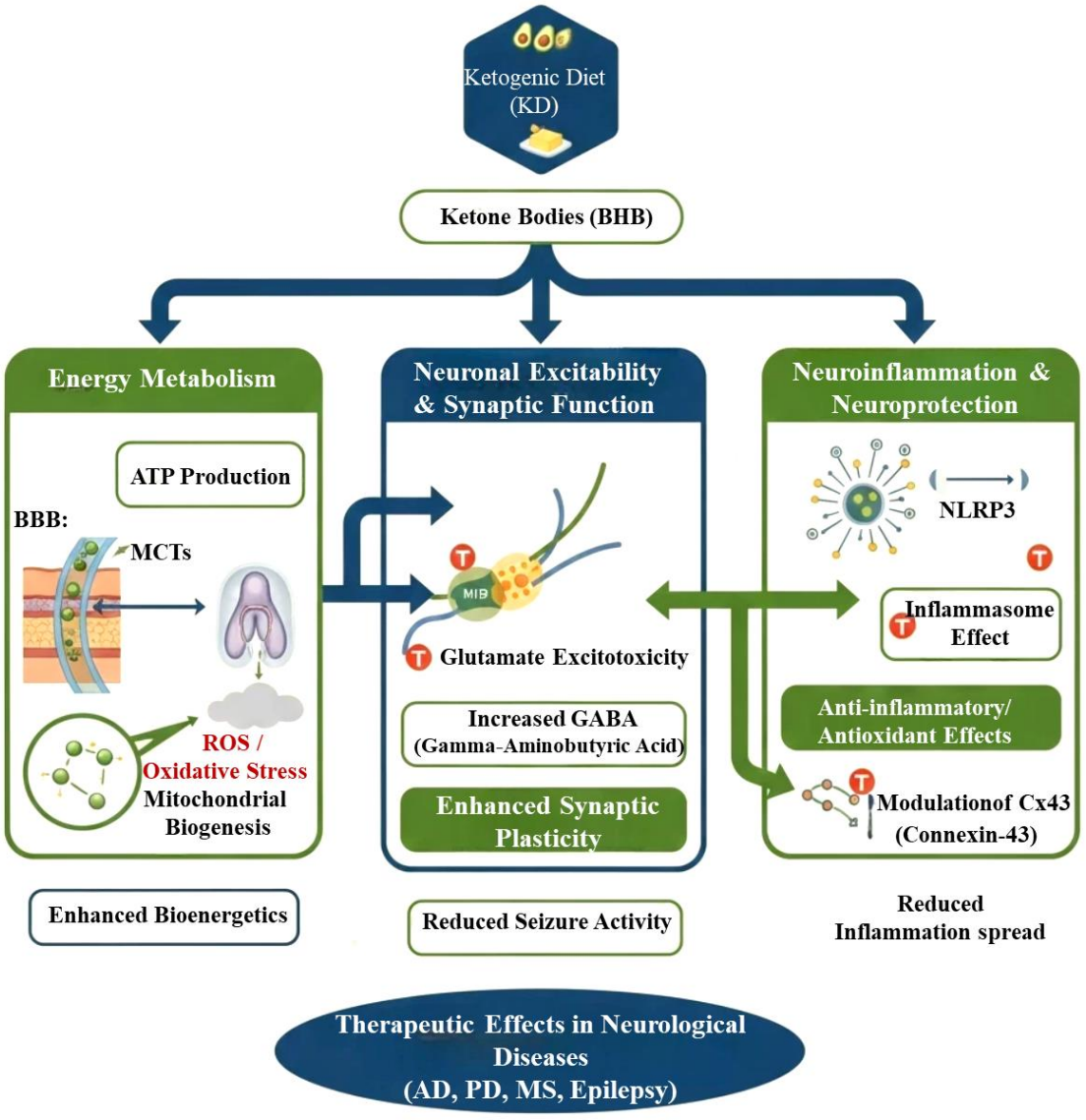

Figure 6. Potential mechanisms of the ketogenic diet effect in neurological diseases. GABA: Gamma-Aminobutyric Acid; BBB: blood–brain barrier; Cx43: connexin-43; MCT: monocarboxylate.

High carbohydrate diet and Alzheimer's disease

Glucose metabolism has been associated with neuroinflammation, but also with AD lesions. Hyperglycemia promotes oxidative stress and neurodegenerative[127]. Cerebral acclamation of amyloidal beta plaque is a classic pathological hallmark of Alzheimer's disease (AD). Cerebral amyloid is present in the brain year before the onset of dementia symptoms and has been suggested

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to be an early trigger of AD process [128]. Nutritional interventions, such as caloric restriction (CR), influence aging and age-related changes in the brain. CR improves cognitive function, including learning and memory, in old rodents [129].

Several studies report that the consumption of high-carbohydrate or fat diet (HFCD) triggers an over generation of reactive oxygen species (ROS) in the brain of rats. In addition, these diets can affect the activity of the antioxidant system[130]. A recent study showed that chronic consumption of HFCD is associated with cognitive impairment in rats, and with impaired antioxidative stress mechanisms and, thus, increased oxidative stress in the hippocampus [131]. Excessive sugar consumption has been linked with obesity, metabolic disorders, diabetes, cardiovascular disease, cancer, depression, and cognitive impairment [132].

Current studies show that impaired glucose metabolism and peripheral hyperglycemia are associated with a higher risk of developing AD. Diet high in glycemic load have been strongly linked to impaired metabolism and an increase risk of type 2 diabetes, which may also implicate diet as a modifiable behavioral factors that affects amyloid aggregation (Taylor et al., 2017). High glycemic diet may stimulate the aggregation of beta amyloid and lead to an increase risk of developing AD in future. High carbohydrate diet, associated with increased blood glucose levels, seems to affect human cognitive functions negatively. However not all carbohydrate have a negative impact on a person's cognitive performance [133].

In animal's models of Alzheimer's disease AD, high sugar diet worsens AD pathophysiology, notably by causing memory impairment and increasing amyloid beta deposits. Studies have shown that consuming a diet high in sugar can impact insulin signaling in the brain, leading to insulin resistance. This could promote the development of dementia and Alzheimer's disease. This is because diets that are high in refined carbohydrates can lead to insulin resistance [134]. During meals, carbohydrates are rarely ingested alone, and their degradation and absorption rates during digestion are modified by the other macro nutrients. Thus meals that are generally higher in refined carbohydrates, such as breakfast and snack, may induce a higher glycemic response and increase the risk of cognitive decline [135].

A study that Investigated the Chinese Alzheimer's disease (AD) population found that high normal fasting blood glucose (BG) level was associated with dementia, independently of vascular risk factors [20]. Greater carbohydrate intake was associated with poorer performance in verbal memory[136]. Evidence also supports a potentially detrimental role of a high carbohydrate diet in conjunction with a diet low in fats and cholesterol. For example Seneff et al. recommend that cholesterol deficiency, alongside high consumption of carbohydrates leads to impaired glutamate signaling, increased oxidative damage and ultimate apoptosis [137].

Conclusion

In conclusion, the role of nutrition in Alzheimer's disease is a promising area of research that has gained increase attention in recent years. While there is no definitive cure for Alzheimer's disease, however eating a healthy diet can help/reduce the risk of developing it. Current research suggests

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that nutritional interventions may be available therapeutic option for both prevention and treatment. A rich diet in fruits, vegetables, whole grains, lean protein and healthy fats can help protect brain and improve overall health. Alzheimer's disease is more common in older adults because it's a degenerative disease that affects the brain over time. Brain cells gradually deteriorate, which can lead to memory loss, confusion, and other symptoms of Alzheimer's disease. Eating a balanced diet can help older adults maintain their health and independence. Diet high in carbs can cause blood sugar level to spike and then crash, which can lead to mental impairment and other negative effects on brain function. High- carbs diets can also increase inflammation and oxidative stress, which can damage brain cells and contribute to cognitive decline. Certain nutrients, which act as antioxidants to protect cell from damaging, such as Vitamin E, Vitamin C, Vitamin B, Carotenoids, and polyphenols, have shown promise in improving cognitive function and reducing risk of Alzheimer's disease. Additionally Mediterranean diet and the ketogenic diet have been shown to be associated with lower risk of Alzheimer's disease. However, more research is needed to determine optimal dietary patterns and nutrient intake for Alzheimer's disease prevention and treatment.

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