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Review

The role of nutritional influence in modifying the risk of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic and neuronal loss. The potential effects of natural compounds on AD have been investigated in the literature. The natural compounds examined include omega-3 long-chain polyunsaturated fatty acids, grape-derived polyphenols, folic acid, vitamin B12, walnuts, raspberries, date seeds, and caffeine. The findings obtained from the studies indicate that omega-3 fatty acids, folic acid, vitamin B12, and vitamin D provide positive effects on nerve cells; walnuts and raspberries offer strong antioxidant properties; and date seeds and caffeine contribute to the maintenance of cognitive functions. It has been stated that these compounds exhibit positive effects through various mechanisms, such as reducing oxidative stress, regulating inflammation, and managing tau protein-related pathologies. In this review, we addressed the potential of natural compounds such as omega-3 fatty acids, B vitamins, walnuts, raspberries, date seeds, and caffeine to prevent AD development and slow its progression and emphasized the importance of current research on this subject.

Keywords: Alzheimer's disease, Vitamin B12, date seed, folic acid, omega-3, polyphenols.

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disorder worldwide, characterized by symptoms such as memory loss, cognitive dysfunction, and difficulties in daily living activities. Key mechanisms involved in the pathogenesis of AD include oxidative stress, neuroinflammation, amyloid-beta (Aβ) accumulation, and tau protein hyperphosphorylation. These mechanisms lead to brain cell damage, loss of synaptic connections, and accelerated neuronal death. Current treatment options for AD focus more on alleviating symptoms rather than halting disease progression. This situation has increased the need for novel approaches in disease prevention and treatment. In recent years, the role of nutrition and nutrients in the pathophysiology of neurodegenerative disorders has garnered significant attention. Various antioxidants, vitamins, plant extracts, and dietary strategies show promise in slowing the progression or alleviating the symptoms of AD. For instance, antioxidant components such as vitamins C and E have been found effective in reducing oxidative stress, and it has been shown that these processes can mitigate the neurodegenerative effects of AD. Additionally, B vitamins (particularly B1, B2, and B3) may play a significant role in slowing AD progression by modulating inflammatory processes and suppressing tau protein hyperphosphorylation.[1]

In addition, the effects of natural compounds and food-derived polyphenols on AD are noteworthy. Walnuts, due to their high phenolic compounds, unsaturated fatty acids, and antioxidant properties, mitigate neurodegenerative processes by reducing oxidative stress. Similarly, raspberry ketone (RK) may be effective in reducing oxidative stress and inflammation, and can aid in managing neurodegenerative changes. Plant-based compounds, such as date seed extract (DSE) and green coffee bean extract (GCBE), have

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the potential to reduce Aβ accumulation and regulate neuroinflammation. Furthermore, caffeine consumption has been shown to slow AD progression by lowering Aβ levels and supporting cognitive functions.[2]

Vitamin D deficiency and oxysterol metabolism (particularly 27-hydroxycholesterol) are significant factors contributing to the pathophysiology of AD. Vitamin D can enhance cognitive performance by regulating oxysterol metabolism through the cytochrome P450 27A1 (CYP27A1) enzyme system. Notably, the combination of vitamin D, folic acid, and vitamin B12 demonstrates synergistic effects that support learning and memory abilities.[3]

In this context, nutrition and specific dietary strategies are thought to make a significant contribution to the management of neurodegenerative disorders such as AD. This study discusses the therapeutic effects of antioxidants, vitamins, and plant-based compounds on AD, focusing on their potential roles in neurodegenerative processes.[4]

NUTRITIONAL INFLUENCE

Diet is a significant non-pharmacological risk modifier for AD. Approaches used to evaluate the role of diet in AD risk include multi-country ecological studies, prospective and cross-sectional observational studies, and laboratory studies. Ecological studies have identified fat, meat, and obesity resulting from high-energy diets as significant risk factors for AD and have reported that AD rates peaked approximately 15-20 years after national dietary changes. Observational studies have compared the Western dietary pattern with the Dietary Approaches to Stop Hypertension (DASH), Mediterranean diet, and Mediterranean-DASH Intervention for Neurodegenerative Delay diets. These studies have identified AD risk factors, including higher consumption of saturated and total fats, meat, and ultra-processed foods, and lower AD risk associated with higher consumption of fruits, legumes, nuts, omega-3 fatty acids, vegetables, and whole grains. Dietary factors associated with a significant risk for AD include inflammation, insulin resistance, oxidative stress, and high homocysteine, and the molecular mechanisms by which components and specific foods influence AD risk are discussed. Given the established food supply systems in most countries, reversing the trend of increasing AD rates will be challenging. However, for those willing and able, a diet low in animal products, abundant in anti-inflammatory, low-glycemic load foods may be beneficial.[5]

Folic acid and vitamin B12

Studies conducted on individuals with AD indicate that nutritional supplements such as folic acid and vitamin B12 contribute positively to treatment by improving cognitive functions and reducing inflammation levels. In AD patients receiving daily supplements of 1.2 mg folic acid and 50 μg vitamin B12 for six months, significant improvements were observed in both cognitive performance and biochemical markers. In assessments related to cognitive performance, it was determined that patients receiving supplements achieved significantly better results compared to those in the placebo group. Specifically, when examining the results of the Montreal Cognitive Assessment test, it was observed that the supplemented group achieved higher scores in subdomains such as naming, orientation, and attention. These findings are considered a strong indication of the supportive effect of folic acid and vitamin B12 supplementation on cognitive functions in AD patients. In terms of biochemical changes, folic acid and vitamin B12 supplementation increased blood folate and vitamin B12 levels. Furthermore, the balance between S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH), which is critical for cellular energy production and methylation processes, was also reported to be restored with supplementation. A notable improvement was observed, particularly in the SAM/SAH ratio. Additionally, homocysteine levels, a harmful substance that negatively affects cell health, and SAH levels were significantly reduced. A significant decrease was also detected in tumor necrosis factor alpha levels, a known indicator of inflammation. These biochemical changes demonstrate that folic acid and vitamin B12 supplementation provides beneficial effects not only on cognitive functions but also on the overall inflammatory state in AD patients. The positive effects of folic acid and vitamin B12

supplementation on cognitive performance and inflammation support the potential use of these nutritional supplements as an adjunctive tool in the treatment of AD patients. The findings obtained indicate that these types of nutritional interventions in AD patients have the potential to slow the progression of dementia and that integrating these interventions into public health policies may be beneficial.[6,7]

Furthermore, an anti-inflammatory dietary model is recommended to improve the overall health of AD patients and reduce inflammation. This model should include foods rich in omega-3 fatty acids, such as salmon, walnuts, and flaxseeds; foods high in polyphenol content, such as olive oil, green tea, and cocoa; and fruits and vegetables like oranges, kiwis, and peppers, which contain potent antioxidants such as vitamins C and E. The addition of spices with natural anti-inflammatory properties, such as turmeric and ginger, to this dietary model may also be beneficial. Adopting a nutrition plan that reduces inflammation and supports cognitive functions, in addition to folic acid and vitamin B12 supplementation, can offer an effective strategy for slowing disease progression and improving quality of life in AD patients. These recommendations should be personalized by a specialist based on individual health conditions and dietary needs.[6,8-10]

Long-chain omega-3 polyunsaturated fatty acids and choline

The n-3 long-chain polyunsaturated fatty acids (LCPUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), include α-linolenic acid obtained from plant sources and EPA and DHA, which are long-chain forms obtained from animal sources. These fatty acids are being investigated for their positive effects on cardiovascular health, inflammation, and neurodegenerative diseases.[11]

Choline, a component of the B vitamin group, is associated with phosphatidylcholine, a building block of cell membranes, and other fatty acids. It is thought to have significant effects particularly on brain health and is suggested to play a role in maintaining cognitive functions and preventing neurodegenerative diseases.[12]

A study hypothesized the selective incorporation of n-3 LCPUFA fatty acids from human plasma into specific lipid species following consumption of n-3 LCPUFA-rich marine fish. Clinical lipidomic analyses revealed that consumption of farmed Atlantic salmon led to a selective increase in phosphatidylcholine and triacylglycerol (TAG) species containing n-3 LCPUFA. High n-3 LCPUFA intake also resulted in changes in cholesterol esters and phosphatidylethanolamines. These findings highlight the importance of differentiating phospholipid and TAG species when assessing disease associations using lipidomic analyses.[13]

In a clinical study, fish oil consumption led to a significant decrease in plasma protein oxidation and hydroperoxide levels. An increase in catalase activity was also observed during the treatment. These results demonstrate the antioxidant effects of omega-3 LCPUFAs and improvements in plasma oxidative stress markers.[14]

Similarly, a prospective, population-based study conducted on middle-aged and elderly men showed that higher choline intake positively affected cognitive performance and reduced the risk of AD. Specifically, phosphatidylcholine intake was associated with a lower risk of AD and better cognitive functions. Analyses showed better results in cognitive tests with higher phosphatidylcholine intake, even when stratified by apolipoprotein E (APOE) phenotype.[15]

Food sources

- **n-3 LCPUFAs:** Fatty fish such as salmon, mackerel, and sardines.
- **Choline:** Eggs, red meat, chicken, and dairy products.

The content of n-3 LCPUFAs and choline is supported by scientific studies for their protective effects against AD. Clinical studies show that high intake of n-3 LCPUFAs and choline leads to improvements in oxidative stress markers and enhancements in cognitive functions.[16,17]

Grape-derived polyphenols

Grape-derived polyphenols are emerging as promising natural bioactive compounds for the prevention and management of AD.

Polyphenols can exert neuroprotective effects by reducing oxidative stress through their potent antioxidant properties, preventing the accumulation of Aβ peptides, and regulating tau protein aggregation.[18,19]

Experimental studies have shown that red wine polyphenols derived from grape derivatives improve AD phenotypes and reduce cognitive decline. For example, polyphenols derived from different grape varieties, such as Cabernet Sauvignon and muscadine, can prevent AD-related cognitive decline by inhibiting Aβ oligomerization and enhancing synaptic plasticity.[20] Additionally, polyphenol extracts derived from grape leaves have been found effective in mitigating the neuropathological mechanisms of AD, such as inflammation and oxidative stress.[21]

Furthermore, adherence to a Mediterranean diet, coupled with regular consumption of grapes and grape-derived products, can reduce the risk of cognitive decline and dementia. This dietary model, by combining foods rich in polyphenols, offers an effective strategy for preventing and slowing the progression of AD It is observed that grape-derived polyphenols act through multiple mechanisms that can contribute to both the pathogenesis and symptom management of AD. In this context, promoting polyphenol-rich dietary habits may be an important approach for the prevention and management of AD. However, a more detailed investigation of the mechanisms and long-term effects in this area is needed.[22]

Tau protein and neurodegenerative processes

Tau protein is an essential microtubule-associated protein that ensures the stability of microtubules in the brain. This protein plays a critical role in the proper functioning of neurons and, under normal conditions, facilitates the assembly and stability of microtubules within cells. However, the hyperphosphorylation of tau leads to a pathological state in neurodegenerative diseases. Hyperphosphorylation disrupts the normal functions of tau, resulting in the breakdown of cellular structures, neuronal damage, and consequently, it is associated with cognitive impairments. Particularly in neurodegenerative diseases such as AD, tau accumulation is observed abnormally in the form of neurofibrillary tangles. In addition to hyperphosphorylation, oxidative stress and inflammatory responses contribute to this pathological state of tau and accelerate the progression of these processes.[23,24]

Oxidative stress contributes to the progression of tau-induced pathological changes. In transgenic animal models, the effects of truncated tau protein have revealed an early process of neurodegeneration, leading to an increase in mitochondrial depolarization and elevated reactive oxygen species. This condition causes oxidative damage and impaired energy production in brain cells. Antioxidant strategies show promising results in reducing tau-related oxidative stress. Antioxidant compounds, such as vitamins C and E, can help prevent the progression of neurodegenerative processes by reducing oxidative damage caused by tau protein. High antioxidant intake supports cellular health in the brain by leading to improvements in oxidative stress markers.[25]

B vitamins may reduce the pathological effects of tau by modulating inflammatory responses. B1, B2, and B3 vitamins have been found to exhibit anti-inflammatory effects and suppress tau hyperphosphorylation by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation in dopamine agonist-stimulated SH-SY5Y cells. These vitamins can also modulate tau-related pathogenic genes such as Glycogen Synthase Kinase-3β and Aβ. By reducing cellular inflammation and supporting neuronal health, B vitamins can limit the impact of tau-induced lesions. This contributes to the regulation of inflammatory processes that trigger tau pathology. Network-based analyses offer an effective approach to identifying genes, transcription factors, and microRNAs (miRNAs) associated with tau pathology. These analyses can be particularly helpful in elucidating the pathogenetic processes related to tau hyperphosphorylation. Genes associated with pathological tau accumulation and the relationships between these genes highlight key pathways that could be targeted in future therapeutic interventions. It has been shown that the transcription factors NF-κB and basic leucine zipper ATF-like transcription factor 3 play significant roles in the regulation

of gene expression. Additionally, eight key miRNAs associated with cognitive impairment have been identified, and these miRNAs have been validated using quantitative polymerase chain reaction. Targeting these miRNAs may prove effective in therapeutic strategies aimed at preventing tau accumulation and halting disease progression. These studies have made important advancements in understanding the pathogenic effects of tau protein and developing treatment strategies, providing guidance for future research. A better understanding of tau's role in neurodegenerative disorders offers critical insights that will support targeted therapeutic approaches.[26]

Dates and caffeine

Nowadays, various nutrients are being studied for their therapeutic potential to slow the progression of AD and, in some cases, alleviate symptoms. In this context, the effects of caffeine, GCBE, and DSE on AD are drawing attention. Caffeine, a compound found particularly in popular beverages like coffee, has been the subject of extensive research in recent years for its potential therapeutic effects against AD. Various scientific studies have shown that caffeine intake can slow the pathological progression of AD by reducing Aβ levels. Moderate caffeine consumption, particularly in reducing serum Aβ levels, has been identified as offering a protective effect against AD. However, it has also been proven that the beneficial effects of caffeine metabolism are not limited to caffeine itself, and its metabolites are not capable of producing these effects.[27,28]

Caffeine-free alternatives, such as GCBE, are also gaining attention for their protective potential against AD. Research conducted on fructose-induced AD rat models has shown that GCBE consumption suppresses beta-secretase-1 levels, thus preventing the accumulation of Aβ plaques. Furthermore, GCBE has been found to reduce oxidative stress and enhance cholinergic activity. This has proven to be effective in improving learning and memory abilities.[29]

Date seed extract also emerges as an effective neuroprotective source against AD. It contains bioactive components such as phenolics, flavonoids, and vitamins, and is notable for its ability to reduce oxidative damage. A study demonstrated that DSE significantly reversed Aβ-induced memory and learning impairments in rats and reduced caspase-3 expression levels. Additionally, DSE was observed to decrease neuronal degeneration in the hippocampal region.

These findings highlight the protective and therapeutic effects of both caffeine and caffeine-free alternatives on AD. Specifically, components such as regularly consumed caffeine-free GCBE and DSE may offer potentially safe and effective protective strategies against AD. Further support from clinical studies would be an important step in delaying the progression of the disease during its early stages.[30]

Walnuts and neuroinflammations

Alzheimer's disease is a progressive neurodegenerative disorder in which the brain gradually loses its function, leading to neurological damage. These processes are closely related to dietary habits, and thus, the potential of a healthy diet to slow the progression of the disease is being investigated. Oxidative stress, an important component of the pathophysiology of AD, is associated with the increase of free radicals and cellular damage. Walnuts, due to their high content of antioxidant compounds (phenolic compounds, unsaturated fatty acids, and peptides), have the potential to reduce oxidative stress. Previous studies have shown that walnut extract decreases lipid peroxidation and protein oxidation by inhibiting the formation of free radicals.[2,31,32]

Walnuts may also be effective in reducing neuroinflammation. Neuroinflammation plays a crucial role in the development of neurodegenerative diseases such as AD. Walnuts inhibit peripheral inflammation by regulating microglial activation of inflammatory components such as Aβ and lipopolysaccharides. Additionally, they manage oxidative stress by lowering free radical levels and enhancing antioxidant defense. Many studies have shown the positive effects of walnut-enriched diets on memory, learning, motor coordination, and anxiety in AD mouse models. Specifically, it has been proven that diets high in walnut content improve cognitive functions and reduce the risk of AD in transgenic AD mice.[31-33]

It appears that foods such as walnuts have the potential to slow the progression of AD. Walnuts may reduce the negative effects of AD due to their antioxidant capacity, neuroinflammation-regulating effects, and cognitive function-supporting properties. Clinical studies support the idea that diets high in walnut content have the potential to delay the onset or slow the progression of AD in the long term.[33]

Raspberries and their potential therapeutic benefits

The relationship between nutrition and obesity in AD is of significant importance. Obesity is a well-established risk factor for many neurodegenerative disorders, and nutritional interventions play a crucial role in the prevention and treatment of AD. In recent years, dietary treatments containing natural components have been researched for their effects on factors influencing these processes. Compounds such as RK may be effective in reducing oxidative stress and neurodegenerative changes due to their antioxidant properties. Obesity can accelerate neurodegenerative processes by increasing inflammatory responses in the brain. Studies conducted on obese rat models have shown that RK supplementation delays the progression of AD by reducing oxidative stress and modulating neurodegenerative changes.[34,35]

Raspberry ketone has been shown to inhibit the enzyme acetylcholinesterase, thereby increasing acetylcholine levels in the brain and supporting cognitive function. Combinations of RK have been found to regulate insulin resistance against obesity, effectively aiding in weight loss and improving lipid profiles. Raspberry ketone also raised serum high-density lipoprotein levels and reduced oxidative stress markers, thereby overall modulating insulin and leptin signaling pathways.[35]

Calorie-restricted diets combined with RK have more effectively eliminated obesity-induced neurodegenerative changes. Natural components such as RK, with their antioxidant properties, show promising results in reducing neurodegenerative changes associated with AD and obesity. When supported by nutritional interventions, combinations of RK play an important role in preserving cognitive function and slowing the progression of neurodegenerative diseases. These findings suggest that RK supplementation, when combined with dietary strategies, could be a potential therapeutic approach for managing AD.[34,35]

Vitamin D deficiency, CYP27A1, and 27-hydroxycholesterol metabolism

Recent studies have shown that factors such as vitamin D deficiency and oxysterol metabolism may play a significant role in the pathogenesis of AD. The oxidized cholesterol metabolite 27-hydroxycholesterol (27-OHC) is a compound synthesized by vitamin D and the CYP27A1 enzyme system. Both vitamin D and 27-OHC are believed to have important roles in AD.[36,37]

Vitamin D deficiency can lead to cognitive decline with aging. Specifically, vitamin D deficiency has been associated with poor cognitive performance and low bone mineral density.[35] This suggests that vitamin D supplementation could be a potential treatment for reducing cognitive impairments in AD. The 27-OHC, regulated through the CYP27A1 enzyme, is an important factor affecting learning and memory abilities. Changes in the expression of the CYP27A1 gene may contribute to the correction of memory disorders caused by vitamin D deficiency.[36,37]

Moreover, the combined use of vitamin D, folic acid, and B12 has played a significant role in improving learning and memory abilities in mice with vitamin D deficiency. Studies have shown that the use of these vitamins, either alone or in combination, positively affects the 27-OHC metabolism by regulating CYP27A1 expression. Research examining the relationship between vitamin D deficiency and AD suggests that these vitamins may play a potential role in AD treatment. Components such as CYP27A1 and 27-OHC play a key role in these mechanisms, and further studies aim to provide a more detailed understanding of these relationships.[37]

Vitamin K

Nutrition plays a critical role in AD, and in recent years, the relationship between

vitamin K deficiency and AD has been a focus of research. Vitamin K plays an important role in many brain functions and in the management of neurodegenerative diseases. Vitamin K deficiency can increase Aβ aggregation observed in AD and accelerate the formation of free radicals. This can lead to toxic effects in nerve cells, resulting in cognitive decline. Studies have shown that modified vitamin K3 analogs can effectively inhibit Aβ aggregation and slow the progression of AD.[38]

Vitamin K deficiency also emerges as an increasing issue with aging. Particularly, individuals carrying the APOE4 genotype are more likely to experience vitamin K deficiency. This condition can lead to a reduction in brain sulfotransferase activity and disrupt communication between nerve cells. Therefore, adequate vitamin K intake is considered an important protective factor against the pathogenesis of AD.[39]

Dietary vitamin K also plays a role in many biochemical processes necessary for brain health. It has been noted that vitamin K deficiency can reduce the function of Gla proteins in the nervous system, leading to a loss of cognitive abilities. Vitamin K can activate antioxidant defense systems, preventing oxidative damage in the brain and thereby slowing the progression of AD.[42]

In addition, the frequent occurrence of vitamin K deficiency during antimicrobial treatment in elderly individuals may worsen nutritional deficiencies. Particularly, multimorbid and frail patients are at risk during situations that require antimicrobial treatment, and vitamin K deficiency can contribute to a decline in cognitive abilities in these patients. Adequate intake of vitamin K through nutrition plays an important role in the management of AD. Dietary vitamin K can slow neurodegenerative processes and help preserve cognitive functions in the brain. Research on vitamin K and other nutrients is crucial for understanding the impact of personalized nutritional approaches on AD.[41]

In conclusion, AD is a serious neurodegenerative disorder commonly observed among the elderly population, leading to cognitive decline and memory loss. It is clear that balanced nutrition plays a significant role in supporting cognitive health and preserving neurological functions. Moreover, natural compounds and specific dietary strategies have shown potential benefits in slowing neurodegenerative processes. Adopting healthy eating habits can be considered an important step in preventing AD and slowing its progression. However, large-scale studies are needed to strengthen the findings in this field.

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