The Role of Antioxidants in Alzheimer's Disease: Effects on Risk and Cognitive Function

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Introduction

With the growing aging population, dementia, a condition marked by devastating cognitive decline, has become a public health crisis, demanding innovative approaches to delay its onset. Dementia is a highly prevalent condition characterized by cognitive difficulties that affect a person's ability to perform everyday activities independently (Manly et al., 2022). As cognitive impairment advances, patients increasingly need care, supervision, and support, often culminating in the necessity for full-time long-term care. The estimated prevalence of dementia in the US in 2020 was 11.3%, affecting about 6.07 million people (Manly et al., 2022). The number of people diagnosed is projected to grow exponentially (almost double every 20 years), shown by Figure 1 below, with a higher burden seen in middle and low income countries. Alzheimer's is the most common form of dementia, seen in 60-80% of those diagnosed (Manly et al., 2022). The two hallmark pathologies required for an Alzheimer's diagnosis include the extracellular plaque deposits of amyloid-beta peptide (Aβ) and neurofibrillary tangles of the microtubule binding protein tau (Murphy & LeVine, 2010). Oxidative stress plays a major role in brain alterations (Terracina et al., 2022).

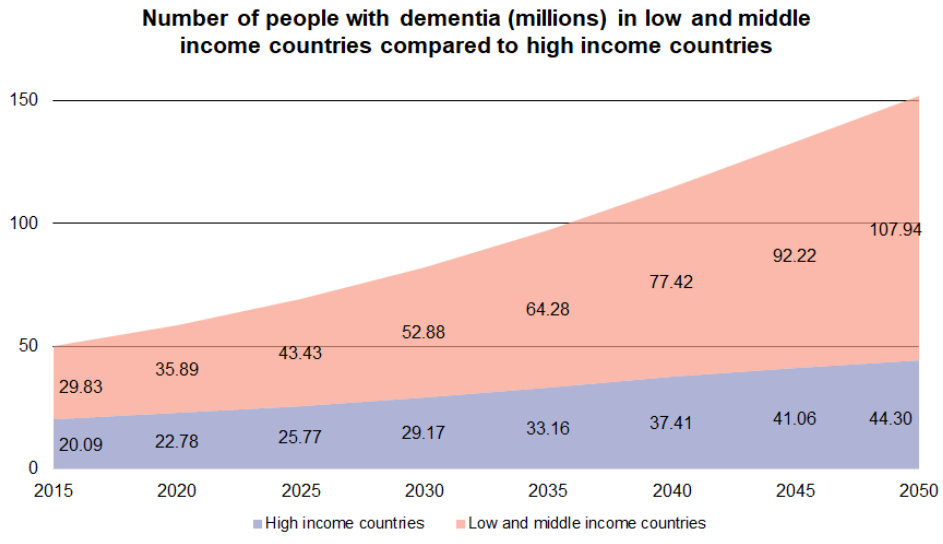

Figure 1: Projection of number of people with dementia over the next 25 years comparing low and middle to high income countries (Alzheimer's Disease International, 2020)

Alzheimer's Disease is a neurodegenerative disease for which no effective treatments exist (Xu Lou et al., 2023). However, certain diets and nutrient-based interventions, such as increased antioxidant intake, have shown potential in delaying disease progression (Arora et al., 2023; Terracina et al., 2022). The key mechanisms involve reducing oxidative stress and inflammation, as well as decreasing the buildup of Aβ peptides (Xu Lou et al., 2023). Over time, our society has become more conscious about our eating patterns and how they affect our health, specifically the development of chronic diseases. Those of particular importance in slowing cognitive decline are the Mediterranean diet, the MIND diet, and the ketogenic diet. Both the Mediterranean and MIND diets feature higher antioxidant content compared to the traditional Western diet. This review explores the role of antioxidantsin potentially delaying the onset and progression of Alzheimer's disease. By examining recent studies on antioxidants such as vitamin E, vitamin C, and plant-derived compounds like hydroxytyrosol and resveratrol, this paper will explore the potential role of dietary antioxidant intake in preventing or slowing the progression of Alzheimer's disease.

Research Methods

In conducting this research, keywords utilized were "Mediterranean diet," "antioxidants," "cognitive function," "cognitive decline," "dementia," and "Alzheimer's" to guide the search across specific databases -- PubMed and the Cochrane Library. This method helped locate high-quality sources that focused on the neuroprotective role of antioxidants. The search yielded mostly systematic reviews, literature reviews, and meta-analyses, which provided a comprehensive view of the current understanding of antioxidants in relation to cognitive health. This literature review includes insights from select reviews, but focuses mainly on individual

studies and the findings that came from them. During the literature search, two articles were unavailable to be read, but their abstract contributions were significant in supporting the thesis that antioxidant intake is linked to cognitive decline (Mullan et al., 2018; Zhao et al., 2024).

For this research on antioxidant-rich diets and Alzheimer's disease, the inclusion criteria focus on peer-reviewed articles, systematic reviews, and clinical trials involving adults aged 50 and older, specifically those diagnosed with or at risk for cognitive decline. The studies must evaluate dietary interventions featuring antioxidants and report on cognitive outcomes. Exclusion criteria eliminate non-peer-reviewed articles, studies involving populations younger than 50, and those that do not focus on dietary antioxidants or Alzheimer's disease.

For the body of this review, a total of 17 peer-reviewed articles were selected and analyzed to assess the impact of antioxidant-rich diets on Alzheimer's disease progression. The articles were systematically categorized based on common findings related to cognitive health and antioxidant consumption. The themes identified include: (1) dietary patterns such as the Mediterranean diet that are rich in antioxidants and their association with Alzheimer’s risk, (2) the role of specific antioxidants like vitamins C and E in cognitive decline prevention, and (3) the case for dietary antioxidant versus supplemental antioxidant intake. Each theme will be explored in detail to provide a comprehensive understanding of the current research landscape.

Dietary Patterns for Cognitive Health

The Mediterranean and MIND diets focus on healthy fats (polyunsaturated fatty acids i.e. omega-3s, olive oils), antioxidants, whole grains, and fruits and vegetables. Following a

Mediterranean or MIND diet is associated with fewer signs of Alzheimer's disease within older adults, and green leafy vegetables, in particular, were associated with less Alzheimer's brain pathology (Agarwal et al., 2023). Here is a brief breakdown of each diet pattern:

1. MIND (Mediterranean-DASH intervention for Neurodegenerative Delay) diet: vegetables, especially green leafy vegetables such as spinach, romaine lettuce and kale; berries over other fruit; and beans, nuts, and one or more weekly servings of fish (Agarwal et al., 2023)
2. Mediterranean diet: vegetables, fruit, legumes, nuts, and at least three servings of fish each week (Agarwal et al., 2023)

These diets overlap in their inclusion of olive oil, whole grains, small amounts of wine, and limited red meat (Agarwal et al., 2023). A post-mortem study which followed older adults from around age 84 until death found that adherence to the Mediterranean or MIND diet was linked to lower levels of amyloid plaques in the brain (Agarwal et al., 2023). Those with the highest intake of leafy greens had less global Alzheimer's Disease pathology compared to those with the lowest intake of leafy greens (Agarwal et al., 2023). Another study concluded that consuming approximately one serving a day (~1/2 cup cooked, 1 cup raw) of green leafy vegetables and foods rich in other antioxidants may help slow cognitive decline with aging (Morris et al., 2018). These dietary patterns not only contribute to overall health but also promote the intake of antioxidant-rich foods, which are crucial for protecting against oxidative stress—a key factor in cognitive decline.

Narrowing in on Antioxidants

Antioxidants act to trap reactive oxygen species and decrease oxidative damage (Terracina et al., 2022). Patients with Alzheimer's exhibit a significantly lower level of the antioxidants, α-carotene, β-carotene, lycopene, lutein, and vitamins A, C, and E, within their plasma compared to cognitively intact individuals (Terracina et al., 2022). Research indicates that low plasma levels of antioxidants are associated with neurodegeneration, with deficiencies in vitamins C and E particularly linked to cognitive disorders (Terracina et al., 2022). Animal and human subject studies demonstrated that dietary interventions and plant-based bioactive compounds with antioxidant effects may help restore memory or delay the onset of memory issues, particularly when stress-related changes are involved (Terracina et al., 2022). Antioxidant supplementation has shown potential in reducing oxidative stress, a key factor in Alzheimer's Disease progression. Studies like Xu Lou et al. have shown that these interventions can improve cognitive outcomes, particularly in early-stage Alzheimer's Disease (Xu Lou et al., 2023).

1a. Hydroxytyrosol

Hydroxytyrosol is a phenolic phytochemical with antioxidant properties found in olive leaves and oil. In animal-model experiments, hydroxytyrosol seems to stimulate neurogenesis (creating new neurons in the brain) by enhancing stem and progenitor cell proliferation and neuron survival (Terracina et al., 2022). Its neuroprotective effects could play a role in reducing the risk of Alzheimer's disease by supporting cognitive health.

1b. Resveratrol

Resveratrol, a natural compound found in foods such as red wine, grapes, and berries, has been studied for its potential to prevent cognitive dysfunction related to brain aging (Terracina et al., 2022). Resveratrol interacts with the gut microbiota to produce

neuroprotective and anti-aging effects, which may help mitigate the risk of Alzheimer's disease by modulating inflammation and promoting neuronal health (Terracina et al., 2022).

1c. Curcumin

Recently, using spices and herbs rich in phenolic compounds with strong antioxidant and cancer-preventive properties, like curcumin (an antioxidant found in the turmeric), has been explored as a nutritional strategy to reduce oxidative damage and neurodegenerative issues linked to aging (Terracina et al., 2022).

1d. Vitamin E (alpha-tocopherol)

Vitamin E, particularly in the form of alpha-tocopherol, is an antioxidant found in nuts, cereals, and a variety of vegetables. From the Shanghai Aging Study which followed participants (aged $\geq$ 60 years) for around 5.2 years, participants with low intake of vitamin E had a significantly higher risk of incident dementia than the highest intake group (IR = 2.8) (Liu et al., 2022). They concluded that vitamin E intake is negatively correlated with dementia risk in older adults, and higher intake of vitamin E in the diet may be beneficial in mitigating dementia risk (Liu et al., 2022).

Collectively, these findings support the notion that dietary intake of antioxidants is vital for maintaining cognitive health, as they may counteract the oxidative damage associated with neurodegeneration (Arora et al., 2023). Moreover, lower antioxidant levels have been associated with greater cognitive impairment in Alzheimer’s patients, further highlighting the potential neuroprotective effects of antioxidant-rich dietary interventions (Mullan et al., 2018; Zhao et al.,

2024). These insights bolster the argument for the effectiveness of antioxidant-based nutritional interventions in improving cognitive outcomes.

The Case Against Antioxidant Supplementation

While there doesn't seem to be a downside to ingesting antioxidants in the diet, one study found that although antioxidant supplementation is safe, it is not recognized as an effective treatment for dementia (Lott et al., 2011). Moreover, one could argue that increasing antioxidant intake through the form of supplements will only place more cognitive stress on an already cognitively stressed population via pill burden. A scoping review found that the burden is felt by both the patient and their caretakers (Lim & Sharmeen, 2018). Caregivers often go to great lengths, such as crushing pills, mixing them into food, and spoon-feeding the resulting mixture to their patients.

Evidence supporting high-dose, long-term antioxidant supplementation for disease protection or prevention remains inconclusive. In one controlled trial, men around the age of 65 were divided into four groups: vitamin E, selenium, a combination of vitamin E and selenium, or a placebo, and followed for 5.4 years, with many continuing for an additional 6 years (Kryscio et al., 2017). In this longitudinal study, no combination of supplements prevented dementia (Kryscio et al., 2017). While dietary antioxidants may offer potential benefits, the evidence for high-dose supplementation remains inconclusive, particularly in light of findings from controlled trials that highlight various methodological limitations, such as participant recruitment challenges and biases related to public perception of supplements (Kryscio et al., 2017). Some epidemiological studies have even indicated that supplements may not only fail to show any clear benefits, but could lead to negative effects, including death (Omaye & Elsayed, 2012).

Such findings may deter healthcare providers from recommending high-dose supplementation. In contrast, increasing antioxidant intake through a balanced, antioxidant-rich diet is a safer, more practical approach that poses fewer risks and may be easier to sustain, making it a preferable option for long-term disease mitigation strategies.

Is Dietary Antioxidant Intake Enough to Prevent or Slow Alzheimer's?

While many studies suggest that dietary antioxidants may offer protection against Alzheimer's disease, the evidence remains mixed and warrants further investigation. Some studies have shown promising results, while others report more ambiguous or null findings. For example, The Shanghai Aging Study found that individuals with adequate vitamin E intake had a significantly lower risk of developing dementia compared to those with the lowest intake (<13.20 mg/day). This indicates that dietary antioxidants could play a protective role in preventing dementia (Liu et al., 2022). Other longitudinal studies discussed in the Liu et al. article report similar findings, reinforcing the potential benefits of antioxidants like vitamin E in reducing dementia risk.

Supporting these results, a 2002 retrospective cohort study from The Rotterdam Study, which followed participants aged 55 and older who were initially free of dementia, found that higher intake of both vitamin E and vitamin C was associated with a reduced risk of Alzheimer's disease (Engelhart et al., 2002). This association was found after many adjustments during the statistical analysis. Participants with the highest antioxidant intake had a significantly lower risk of Alzheimer's compared to those with the lowest intake (Engelhart et al., 2002). However, no significant relationship was found between beta-carotene or flavonoid intake and Alzheimer's risk, suggesting that not all antioxidants have the same protective effects.

In contrast, the Nurse's Health Study provided conflicting results, showing limited association between vitamin E, vitamin C, or total carotenoid intake and cognitive decline (Devore et al., 2013). Interestingly, higher lycopene intake was linked to slower cognitive decline, while lower vitamin C intake was also associated with more favorable cognitive outcomes—highlighting the complexity of antioxidant impacts on brain health (Devore et al., 2013).

Each of these studies relied on food frequency questionnaires, a tool prone to systematic error, which could influence the results. While these studies offer valuable insights into the potential protective effects of long-term antioxidant intake, more research is needed to conclusively determine whether dietary antioxidants can prevent or slow the progression of Alzheimer's disease. Future research should continue to explore which specific antioxidants, if any, have the most significant impact on Alzheimer's risk.

These differing results are significant because they highlight the complexity of dietary interventions in neurodegenerative research and underscore the need for further investigation into how specific dietary patterns, antioxidant types, and individual variability may influence cognitive outcomes. Understanding these nuances is essential for developing effective nutritional strategies to mitigate the risk of Alzheimer's disease and promote cognitive health across diverse populations.

The Cost of Cognitive Decline

With the projected rise of people living with all forms of dementia, the financial and societal impacts of the disease are staggering. In 2020, Alzheimer's alone accounted for $305 billion in healthcare costs, a number expected to exceed $1 trillion as the population ages (Wong,

2020). The direct costs associated with Alzheimer's disease include skilled nursing care, home healthcare, and hospice care (Wong, 2020). The indirect costs, which are currently underestimated, include quality of life and informal caregiving, and are associated with significant societal and personal burden (Wong, 2020).

While genetics play a crucial role in determining an individual's susceptibility to Alzheimer's, environmental and lifestyle factors, such as diet, are increasingly recognized for their potential in delaying disease onset or progression ("Alzheimer's Disease Genetics Fact Sheet," 2023). Given these realities, identifying cost-effective interventions, like antioxidant-rich dietary strategies, could dramatically ease both the financial strain and the human suffering associated with Alzheimer's. Implementing these interventions early—particularly for those genetically predisposed—may act as a protective factor, reducing oxidative stress and offering a proactive approach to mitigating the risks of cognitive decline. Nutritional approaches that mitigate oxidative stress offer a promising avenue for reducing these costs while enhancing the quality of life for millions.

Summary

This literature review explored the potential of dietary antioxidants to prevent or slow the progression of Alzheimer's disease, focusing on key antioxidants like vitamin E, vitamin C, and plant-derived bioactive compounds such as hydroxytyrosol and resveratrol. Several studies, including the Shanghai Aging Study and The Rotterdam Study, suggest that higher intake of certain antioxidants, particularly vitamin E, may be associated with a reduced risk of developing Alzheimer's or other forms of dementia. These findings highlight the potential neuroprotective role of antioxidants in reducing oxidative stress, a known contributor to Alzheimer's pathology.

Additionally, diets rich in antioxidants, such as the Mediterranean and MIND diets, are associated with better cognitive health outcomes and lower rates of Alzheimer's disease.

However, conflicting results from studies like the Nurse's Health Study indicate that the protective effects of antioxidants are not uniformly observed across different populations and types of antioxidants. For instance, while vitamin E and C showed promise in some studies, beta-carotene and flavonoids were not consistently linked to a reduced risk of Alzheimer's, and in some cases, vitamin C was associated with unexpected results.

One major limitation in the current body of research is the reliance on observational studies and food frequency questionnaires, which are prone to measurement error and confounding factors. Furthermore, most controlled studies are limited by their short follow-up periods, making it difficult to draw definitive conclusions about the long-term effects of antioxidant intake on Alzheimer's risk and cognitive decline. Another limitation is the variability in the types of antioxidants studied, making it challenging to determine which specific compounds offer the most significant benefits. Furthermore, many antioxidant-rich foods, such as fruits, vegetables, and nuts, also contain other beneficial components like fiber and anti-inflammatory compounds. This makes it difficult to isolate the effects of antioxidants from the broader health benefits of these foods, complicating efforts to pinpoint which factors are responsible for the observed improvements in cognitive health.

Future research should prioritize examining the effects of long-term antioxidant intake through longitudinal studies. By gathering extensive intake data over time and making inferences about its relationship to Alzheimer's development and progression, researchers may gain a better understanding of how consistent dietary patterns impact cognitive health. This approach would

provide deeper insights into how antioxidants contribute to Alzheimer's prevention, allowing for more accurate and nuanced recommendations.

Additionally, interdisciplinary approaches involving dietitians, healthcare providers, and public health officials are essential for effectively promoting antioxidant-rich diets. Collaborative efforts can help create comprehensive strategies that not only raise awareness but also support individuals in making informed dietary choices to enhance cognitive health.

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