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Does The Mediterranean Diet or Botanicals Influence Alzheimer's Disease?

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Dementia is a condition that currently affects over 46 million people worldwide [1]. It is a growing problem of epidemic proportions and while efforts are being made to treat it, the prevalence is estimated to affect over 131 million by the year 2050 [1]. Alzheimer's disease (AD) is the most common form of dementia seen today, comprising 60-70% of all diagnosed cases of dementia [2]. The purpose of this editorial is to review the potential benefits of the Mediterranean diet and some botanicals on AD.

Alzheimer's is characterized by severe cognitive impairment, affecting many vital functions such as memory, reasoning and judgment, language, learning capacity, and comprehension [2]. Alzheimer's usually affects elderly people over the age of 65, though some rare forms have been found to affect individuals under the age of 40 [2]. In the first or second year of the disease, patients often become forgetful and lose some short-term memory, have mild difficulty communicating, become lost in familiar surroundings, as well as some difficulty reasoning and making decisions [2]. Some patients also experience a slight change in mood or behavior [2]. When compared to other chronic diseases, patients with Alzheimer's or other forms of dementia often require a higher degree of care [1].

Anatomy of Alzheimer's Disease

The most common, and main hallmark of the disease, is the aggregates of β-amyloid protein [3]. The β-amyloid protein itself is thought to be toxic to the brain and cause cell death [4]. The toxic form of the protein begins as the Amyloid precursor protein (APP), which is then cleaved by the enzyme β-secretase [5]. Then, the product of the cleavage is cleaved again by γ-secretase, which is thought to produce the toxic Aβ42 byproduct [5]. The Aβ42 byproduct is insoluble and generally forms the senile plaques [5]. The main mechanism of β-amyloid cytotoxicity is believed to be that the plaques destabilize calcium homeostasis in the brain by causing an influx of calcium ions and via interference with the synaptic transmission of acetylcholine. It also causes inflammation in the brain leading to the production of reactive oxygen species [4]. The reactive oxygen species then cause oxidative stress, damaging mitochondria, also a cause of cell death [4].

Another major hallmark of AD is the so-called Tau neurofibrillary tangles, which form inside the neurons. Tau is a protein commonly found in microtubules and plays a major role in a cell's structure [5]. The tau protein can undergo a process of hyperphosphorylation, which causes the tau to be released from the microtubules where it then aggregates into tangles. This both destabilizes neuronal structure as well as inhibits the transmission of neurotransmitters like acetylcholine [3,5].

The Mediterranean Diet

Out of the numerous potential risk factors for Alzheimer's disease, the diet is one of the most prevalent. The Mediterranean diet is thought to be associated with a decreased risk for several chronic diseases such as cardiovascular disease and cancer [6]. While many studies on the subject have been conducted, it is yet unclear what definitive effect a Mediterranean diet might have on cognitive function [7,8]. A Mediterranean diet is largely characterized by a high intake of vegetables, fruit, legumes, cereals, monounsaturated fats accompanied with a low intake of saturated fats, and fish. It also includes a relatively low intake of meat and dairy products and a moderate intake of wine with meals. When broken down into individual parts, a Mediterranean diet offers numerous health benefits, such as omega-3 from fish, antioxidants from fruits and vegetables, vitamin B12, and monounsaturated fatty acids like olive oil [8]. The antioxidants in particular are a current area of study for the reduction or prevention of cognitive decline. A possible insight into why this type of holistic diet may be more protective than any one aspect alone, is that many of the complex food combinations are likely synergistic in nature when it comes to health benefits [9,10].

In several studies, the Mediterranean diet was found to have a positive effect on cognitive decline and the incidence of AD. In large, non-Mediterranean populations over several years, a general decrease in the risk or incidence of AD was associated with a higher adherence to a Mediterranean diet [7,8]. However, in other studies, even high adherence did not result in significant changes in cognitive decline [8]. It is hypothesized that while a Mediterranean diet may have a positive or even preventative effect on the incidence of AD, the benefits decrease with onset of the disease and produce little to no effect on late stage AD [8]. One study conducted on a French population observed an overall decline in annual cognitive dysfunction with higher adherence to the diet but saw no other significant improvements [8]. The same study suggests that a Mediterranean diet may only be cognitively beneficial prior to five years preceding the diagnosis of AD [8]. In a study analyzing the effect of a Mediterranean diet on both AD and mild cognitive impairment, it was found that a higher adherence to the diet resulted in a significantly decreased risk for both [7]. However, there was no significant difference between mild cognitive impairment and AD [7]. This suggests that a Mediterranean diet may have a general protective effect on cognitive function but may not be specifically beneficial to AD patients. It should also be noted that the study was performed on an isolated Australian population and achieved much the same results as previous studies performed in the US and France [7]. Despite the growing evidence for a correlation between a high adherence to a Mediterranean diet and a decreased risk of AD, other results are unclear and inconclusive [11]. This has led to the possibility that the diet may not be an effective tool against AD or that there may be other factors at work.

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While many studies agree, at least to some extent, that a Mediterranean diet provides a protective affect against the risk and incidence of AD, the method of action is largely unclear. As mentioned previously, the possible action of antioxidants in reducing oxidative stress may be a possible mechanism of action. Another possibility, is that it acts by reducing inflammation and metabolic irregularities, two prominent biomarkers for AD [12]. A study was done to determine the possible effect on high-sensitivity C-reactive protein for inflammation, and fasting insulin and adiponectin for metabolic irregularities [12]. However, there was no significant correlation between the diet and the three biomarkers studied [12]. This study does not rule out the possibility that the diet's protective effect may act through an inflammatory or metabolic pathway. Another study determined that the Mediterranean diet did not act through vascular pathways [13].

Another facet of the Mediterranean diet rarely considered is the use of herbs and spices that could also lend health benefits and may be part of the reason that the diet is so promising in research. One of the common herbs utilized in the diet is parsley. This herb has a high content of Vitamin C and Vitamin B12. It is also known to have an anti-inflammatory effect, with inflammation being one of the detrimental conditions of AD. Saffron, Thyme, Basil, Rosemary, Oregano, Sage, and Cilantro along with numerous other spices are also common in Mediterranean food.

Botanicals

Bacopa monniera

The plant is also known as water hyssop which is a creeping herb found predominantly in India [14,15]. It has been known in Ayurveda, traditional Indian medicine, to improve concentration and memory while also enhancing overall cognition [15]. One study found that an ethanol extract of Bacopa monniera can help reduce the effects of oxidative stress on the brain [15]. It is thought to have a neuroprotective effect and most of its constituents are thought to be synergistic. Its main constituents are bacosides. These compounds improve nerve impulse transmission [14].

Ginkgo biloba

It is common in Traditional Chinese Medicine (TCM). It has been known to have some antioxidant activity as well as decreasing the neurotoxic effects of nitric oxide [16,17]. It was also found to protect against the toxicity of other peroxides implicated in β-amyloid toxicity while also reducing β-amyloid toxicity directly. This is attributed to its composition of flavonoids [18]. The same study showed that Ginkgo acts in a dose-dependent manner to exert a neuro-protective effect against β-amyloid toxicity. A terpenoid extract from Ginkgo biloba also showed a neuro-protective effect against brain ischemia, which is implicated in AD pathology [19]. In a much more general sense, Ginkgo has been found to improve memory in mice, both young and old [20]. Some studies have found that Ginkgo had a mild benefit similar to other acetyl cholinesterase inhibitors currently on the market, while others have found no significant improvement in cognition [21,22]. It appears that Ginkgo has the most significant effect in the early stages of the disease [23].

Huperzine A

It is a compound found in Huperzia serrata, a moss commonly used in TCM [22]. In TCM, Huperzia serrata is mainly used to enhance memory function [24]. It is also thought to have a neuroprotective effect with the ability to reduce the effects of oxidative stress [22,25]. Huperzine A has also been shown to regulate the expression of apoptotic proteins and affect amyloid precursor protein metabolism [25]. It is a potent and reversible acetylcholinesterase inhibitor [24,26]. Currently, Huperzine A has been approved as a memory enhancing dietary supplement [26]. In a clinical setting, it has been shown to improve cognition with few side effects [27]. It should be noted that one study found Huperzine A to be more potent than both donepezil and rivastigmine (drugs for AD) in increasing acetylcholine levels in the brain and had a longer lasting effect [28]. While Huperzine A appears promising, it has mostly only been tested in China and more studies are needed to determine its effect on Alzheimer's patients.

Rosemary

The herb was commonly used by the Greek and Roman civilizations as a memory enhancer [29]. It is most commonly known for its antioxidant activity, as it has over two dozen different antioxidant constituents, most notable rosmarinic acid [24]. It is a modest acetylcholinesterase inhibitor with an activity below that of both sage and lemon balm [30]. Rosemary has been found to increase alertness, reduce anxiety, and improve cognitive function [31,32].

Sage

It is an herb commonly used in Europe to enhance memory and cognition [22]. It has antioxidant activity, mainly from carnosic and rosmarinic acid which help protect against oxidative damage [24]. Sage has anti-inflammatory constituents and acts as an acetylcholinesterase inhibitor [33-35]. Sage extracts have been found to improve cognition both in healthy young adults and in patients with mild to moderate Alzheimer's [36-40]. It also has anti-butyrylcholinesterase activity, making it doubly active [41,22]. One study found that sage reduced the amyloid burden in vivo and had a neuro-protective effect against amyloid cytotoxicity due to rosmarinic acid [42].

Turmeric

This Indian spice has anti-oxidant activity [24]. The active ingredient in Turmeric is curcumin which also has anti-inflammatory activity [43]. One study found that it even reduced the amyloid burden in transgenic mice [43]. Another study suggested that there is epidemiological evidence that turmeric-filled diet is associated with improved cognitive performance as well as a lower prevalence of AD [44,22]. Curcumin was also found to prevent the oligomerization and aggregation of β-amyloid in a mice model [45].

Lemon balm

Melissa officinalis, more commonly known as lemon balm, has been used throughout Europe for centuries for its anti-depressant properties and memory enhancing capabilities [22]. It is a weak acetylcholinesterase inhibitor, largely coming from rosmarinic acid [24]. It also has antioxidant properties and has been shown to improve cognition in a clinical setting [24]. Melissa extracts have the capability to bind to nicotinic, muscarinic, and $GABA_A$ receptors [46,47]. In a clinical setting, lemon balm extracts were found to reduce cognitive impairment in patients with Alzheimer's [29].

In conclusion, AD is a growing problem globally. The Mediterranean diet and herbal remedies could play a role in controlling this disease.

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