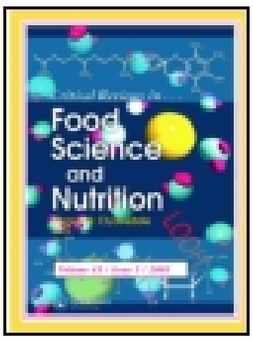

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Neuro-nutrients as anti-Alzheimer's disease agents: A critical review

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ABSTRACT

Alzheimer's disease (AD) is characterized by a massive neuronal death causing memory loss, cognitive impairment and behavioral alteration that ultimately lead to dementia and death. AD is a multi-factorial pathology controlled by molecular events such as oxidative stress, protein aggregation, mitochondrial dysfunction and neuro inflammation. Nowadays, there is no efficient disease-modifying treatment for AD and epidemiological studies have suggested that diet and nutrition have a significant impact on the development of this disorder. Indeed, some nutrients can protect all kind of cells, including neurons. As prevention is better than cure, life style improvement, with a special emphasis on diet, should seriously be considered as an anti-AD track and intake of nutrients promoting neuronal health is the need of the hour. Diets rich in unsaturated fatty acids, polyphenols and vitamins have been shown to protect against AD, whereas saturated fatty acids-containing diets deprived of polyphenols promote the development of the disease. Thus, Mediterranean diets, mainly composed of fruits, vegetables and omega-3 fatty acids, stand as valuable, mild and preventive anti-AD agents. This review focuses on our current knowledge in the field and how one can fight this devastating neurodegenerative disorder through the simple proper modification of our life style.

Key words: Alzheimer's disease; Neuroprotection, Diet, Nutrition, Vitamins, Polyphenols, Mediterranean diet

Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are age-related pathologies, which, beyond the obvious impact on patients, are associated with the financial burden on caregivers and families in addition to physical and mental stress (Hung et al., 2010). The number of AD patients in the world is estimated to 46.8 million and is expected to increase up to 131.5 million by 2050 (Wieckowska et al., 2016). Such remarkable numbers have heavy financial burden to the society and on the individuals concerned with care and treatment, including families (Olesen et al., 2012). Despite many decades of AD research, the principal prescribed treatments for AD (cholinesterase inhibitors and NMDA receptor antagonists) only alleviate the symptoms, and display numerous heavy side effects (Lindsley, 2012; Park and Stacy, 2015).

AD is the most common cause of dementia worldwide and is defined as a multifactorial neurodegenerative disorder with progressive loss of short and long term memory resulting in difficulties in daily living (Scheltens et al., 2016). Several complex pathogenic processes are involved in the progression and development of the disease, including inflammation and oxidative stress, altogether leading to neuronal death and cholinergic deficits (Dastmalchi et al., 2007). In AD, beside the hyperphosphorylation of the microtubule-associated tau protein leading to the production of intraneuronal neurofibrillary tangles (NFT), the amyloidogenic Aβ peptide misfolds and self-aggregates to form transient low molecular weight soluble oligomers, β-sheet rich protofibrils and ultimately high-ordered insoluble fibrillar structures giving rise to the formation of extracellular senile plaques (Yankner, 1996). This abnormal conversion of a native,

non-toxic protein structure into toxic aggregates hence classifies AD as a "protein misfolding disorder".

Current pharmacological strategies for the treatment and management of AD include the use of cholinesterase inhibitors. Rivastigmine, donepezil and tacrine are FDA-approved drugs for clinical use in the US which increases acetylcholine levels in AD brain. However, continuous usage of these drugs causes side effects such as vomiting, dizziness, nausea and gastrointestinal disorders (Ali et al., 2015). Additionally, most of the prescribed drugs used for the treatment of AD are targeting one single AD-related feature. However, some developed multi-targets synthetic agents have so far shown low pharmacological activity *in vivo* because of their poor absorption, due to their inability to efficiently pass through the blood brain barrier (Youdim and Buccafusco, 2005). Since AD is a complex multifactorial neurodegenerative disorder and because it involves diverse pathological mechanisms, biologically active natural compounds with multiple targets can indeed be considered as promising anti-AD preventive agents.

Beside age, risk factors of AD mainly include family history (rare genetic early-onset forms of the disease), the presence of the apolipoprotein (ApoE4) gene and any head injuries. In the current scenario, nevertheless, a growing number of additional risk factors for AD, including diabetes, obesity, hypertension, smoking, depression, as well as cognitive and physical inactivity have been evidenced (Barnes and Yaffe, 2011). Interestingly, many studies across the world have shown a correlation between dietary patterns and AD incidence, thereby indicating diet as a modifiable risk factor and The National Institute on Aging–Alzheimer's Association guidelines for Alzheimer's disease (AD) and cognitive decline due to AD pathology introduced some evidence suggesting a direct relation between diet and changes in the brain structure and activity.

In this context, many related claims have been made that increasing adherence of Mediterranean diets (MeDi**)**, low consumption of alcohol, lower consumption of carbohydrates, higher consumption of polyunsaturated fatty acids (PUFA) and increased vitamin intake are lessening the risk of developing AD (Engelhart et al., 2002; Morris et al., 2003b; Seneff, Wainwright, and Mascitelli, 2011; Gardener et al., 2012; Piazza-Gardner, Gaffud, and Barry, 2013; Willett, Devries, and Van Horn, 2015). Interestingly, other emerging dietary patterns such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets were associated with slower rates of cognitive decline and significant reduction of AD rate and have been suggested as possible anti-AD diets and there was also accumulating evidence that combinations of foods and nutrients into certain patterns may act synergistically to provide stronger health effects than those conferred by their individual dietary components (Solfrizzi et al., 2017). Yet, such a heterogeneity in claims contributes to substantial confusion in the field and complicates proper recommendations in clinical practice.

Since the time of ancient Greece, lifestyle changes such as diet and exercise have been shown to noticeably prevent or manage many diseases. A concept that Hippocrates nicely formulated as "Let food be your medicine, let medicine be your food" (Leonti, 2012). Since then, it has been shown that beneficiary dietary patterns play important roles in fighting against AD as thoroughly and previously reviewed (Ramesh et al., 2010). Recently, studies have evidenced that there is a real association between lifestyle changes, such as diet and dietary components and the occurrence of AD (Albarracin et al., 2012; Vassallo, 2015) and it has been reported that there is a strong correlation between poor nutrition and AD (Polidori, 2014). Hence, the consumption of dietary supplements and nutraceuticals could be effective therapeutic tracks for AD treatment.

Thus, recent anti-AD experimental approaches have focused on the use of dietary supplements and natural source/products with multi-neuroprotective roles, which display little or no side effects when compared to synthetic molecules.

Currently, there are no validated approaches able to successfully prevent or delay the progression of AD. Thus, acting on multiple targets by means of natural edible compounds opens up a new window for early intervention and gained more and more interest in the past years (Vassallo, 2015). In this regard, following appropriate dietary patterns is highly relevant regarding neuronal protection and goes beyond their well-established antioxidant properties. The aim of this review is to highlight the correlation between healthy diet and AD protection, with a particular emphasis on higher adherence to Mediterranean diet, the beneficial effects of which being conveyed by several bioactive compounds and to update our current knowledge of the mechanisms sustaining such an association.

Methodology and illustrations

Well-known scientific search engines such as viz., Google Scholar, Pubget, Medline, PubMed, EMBASE, Mendeley, Science Direct, Scopus and Springer Link were used to retrieve online literature. The results were then cross-referred to generate a total number of 252 references cited in this review (mostly covering the period 1986-2017). **Table 1** summarizes the so far published works dealing with the impact of Mediterranean diets on cognition and in Alzheimer's disease in human clinical trials. **Table 2** shows the effects of individual nutrients present in MeDi on AD in human clinical trials. **Figure 1** underscores the factors, including MeDi, which stand as either risk or protective ones regarding AD. The impact of neuro-nutrients

on the control of oxidative stress have been enlightened in **Figure 2** and **Figure 3** illustrates the protective effects of MeDi on Alzheimer's disease.

Role of diet in Alzheimer's disease

Several studies have reported significant benefits of healthy nutrition on neurodegenerative disorders (Eskelinen et al., 2011; Gillette-Guyonnet, Secher, and Vellas, 2012) and it has been shown that diet may play a key role in the causation and prevention of AD since dietary modifications in animals could extend their life span by increasing the resistance of neurons to degeneration (Mattson, 2000). Hence, diet, which is an easily modifiable environmental factor, has recently aroused a growing interest concerning its possible impact on AD. It has been reported that a higher dietary intake of vitamin C, E, $B_{12,}$ flavonoids, antioxidants and folate can reduce the risk of developing AD (Scarmeas et al., 2006a). However, because foods are consumed as part of a whole daily diet and not consumed individually, there are a very limited number of studies reporting on the effect of dietary patterns on AD. Moreover, interactions between the components of a diet may add to the complexity of studying the effect of diet on one given pathology (Scarmeas et al., 2006b; Gu et al., 2010; Hu et al., 2013). Indeed, current studies investigating the effect of individual foods on the risk of AD have shown inconsistent results, partly because people eat meals with combination of different nutrients that may have additive and/or synergistic effects (Luchsinger, Noble, and Scarmeas, 2007; Feart et al., 2013). In this regard, defining diet by "dietary patterns" allows to capture its multidimensionality and certainly helps understanding the genuine impact of nutrition on AD.

Mediterranean diets and their impact on AD

Mediterranean diet (MeDi) is a new recommendation based on dietary patterns from Greece, France, Southern Italy and Spain in 1940s and 1950s (World Health Organization, 2009). According to the "Global Strategy on Diet, Physical Activity and Health", a review by the World Health Organization (WHO), MeDi is a promising approach to prevent many diseases and to increase the quality of life (World Health Organization, 2009). MeDi was first investigated by Ancel Keys during his seven countries study in 1950s, in which a large prospective cohort study involved more than 11,000 participants (Keys et al., 1986). MeDi includes high consumption of plant-based foods (i.e., vegetables, fruits and cereals), a moderate to high intake of fish, low consumption of meat and poultry, low to moderate intake of dairy products together with an adequate intake of olive oil as the main source of fat and a regular intake of red wine during the meals. Hence, MeDi seems to include many of the potential components reported as beneficial for AD and cognitive functions (Sofi et al., 2010).

Subsequent epidemiological studies confirmed Key's findings by reporting a multitude of health benefits of MeDi, including beneficial effects on chronic diseases thereby decreasing mortality worldwide (Couto et al., 2011; Gu and Scarmeas, 2011; Lopez-Garcia et al., 2014; Gotsis et al., 2015). Meta-analysis studies showed that the individuals who adhere to the MeDi display better health status and show a reduced rate of overall mortality (9%), cardiovascular diseases (9%), cancers (6%), PD and AD (13%). Altogether, these studies clearly underline the possible use of MeDi for public health, as an initial prevention strategy for major age-related diseases (Thaipisuttikul and Galvin, 2012).

A prospective cohort study on a 2,258 individual's non-demented community showed that higher adherence to MeDi correlates with a considerable reduction in the risk of developing AD. Indeed, individual foods were not significantly associated with risk for AD, except the MeDi

pattern, since a greater adherence to the MeDi considerably reduced risk of AD (Kawas, 2006; Scarmeas et al., 2006a).

As a matter of fact, the individuals who adhered to medium and high MeDi had a respective 15 to 21% and 39 to 40% reduction in developing AD and each additional unit of adherence further reduced the risk of developing AD by 9 to 10% (Kawas, 2006; Scarmeas et al., 2006a). In addition, Samieri and colleagues established that the long-term adherence to MeDi was associated with a significant improvement of cognitive functions and memory and found that greater adherence delayed cognitive aging by approximately 1 year (Samieri et al., 2013). Furthermore, higher adherence to MeDi might prevent/control disturbances in insulin/glucose metabolism that can result in type II diabetes mellitus (DM-II), which is also considered as a major risk factor for cognitive impairments and AD (Biessels et al., 2006). Also, in the absence of DM-II, chronically elevated blood glucose levels were found to have a negative impact on AD and memory in older adults (Crane et al., 2013; Kerti et al., 2013) and higher adherence to MeDi was associated with a reduced risk of developing Mild Cognitive Impairment (MCI) and conversion of MCI to AD, thus suggesting that prophylactic interventions may reduce the risk of developing prodromal stage of the disease (Scarmeas et al., 2009; Arab and Sabbagh, 2010). Related to this, a report from the Mayo clinic (MN, USA) found that higher consumption of vegetables and unsaturated fatty acids reduced the risk of MCI (Thaipisuttikul and Galvin, 2012).

Moreover, Feart et al. described that MeDi has a beneficial effect by slowing down cognitive impairment and delay the onset of AD during the 5 years preceding the clinical diagnosis of AD (Feart et al., 2009). Therefore, MeDi would be effective at least 5 years before the clinical diagnosis of dementia, when AD pathology and neuronal loss are still limited (Feart et al., 2009; Vassallo and Scerri, 2013). Although most of the research studies carried out with MeDi have

been conducted on mediterranean populations, some reports also showed beneficial effects of this diet in non-mediterranean countries (Donini, De Felice, and Cannella, 2007). A study by Gardener et al. also found that MeDi has a protective role in different multiethnic populations (Gardener et al., 2012). These results strongly suggest that the protective power of MeDi is not dependent on the genetic backgrounds and can apply to a large number of populations, a hypothesis further demonstrated by other studies conducted in India and in Northern Europe leading to similar conclusions (Scarmeas et al., 2007).

In summary, adherence to MeDi has been clearly shown to have positive effects on reducing the risk of developing AD and on cognitive functions during aging, mainly via beneficial effects on lipid and glucose metabolism. As a further step forward, animal-based studies have then identified MeDi-contained specific individual nutrients that exert protective effects on the aging brain (Alles et al., 2012). Because MeDi is a complex eating pattern, it is also conceivable that one single component could convey multiple beneficial effects (Jacobs Jr, Gross, and Tapsell, 2009; Gotsis et al., 2015). Therefore, understanding their peculiar mechanisms of action would certainly help developing preventive anti-AD therapies. In the up-coming section, we propose to discuss the properties of some of the components present in MeDi and their possible therapeutic usefulness in AD.

Components of Mediterranean diets and their impact on AD

Red wine

Wine is an alcoholic beverage made from grapes, fermented without the addition of sugars, acids, enzymes, water, or other nutrients (Johnson, 1989). Red grapes are a major source of polyphenols when compared with white grapes (Cantos, Espin, and Tomas-Barberan, 2002) and

for this reason, the consumption of red wine has been showed to have a beneficial impact on many diseases. The protective role of moderate intake of red wine is widely recognized (Tangney et al., 2011b) and moderate red wine intake, mostly during meals (one glass/meal), is one of the key aspect of MeDi (Arab and Sabbagh, 2010). Pasinetti and Eberstein suggested that a diet rich in protein, fruits and vegetables, together with moderate wine consumption would help to normalize the blood sugar and successfully provide antioxidants (Pasinetti and Eberstein, 2008) and an epidemiological study has very recently reported that moderate intake of red wine, exclusively as part of a holistic MeDi, resulted in a decrease in AD symptoms (Caruana, Cauchi, and Vassallo, 2016). Additional works have established that moderate wine drinkers (two glasses/day for men and one glass/day for women) have a reduced risk of developing AD and display improved cognitive functions when compared to non-drinkers (Pasinetti and Eberstein, 2008; Arab and Sabbagh, 2010). In the meantime, Luchsinger et al. found that intake of beer and liquor does not convey neuroprotection, thereby indirectly confirming the polyphenol-dependent effect of red wine (Luchsinger et al., 2004) while individuals aged 65 and above who consumed three servings of wine per day over years had lower risk of developing AD when compared to age-matched controls (Vassallo and Scerri, 2013). Among the red wine-contained polyphenols, resveratrol is the most abundant one. Because of its powerful antioxidant activity, it logically emerged as one possible anti-AD active compound of red wine. Indeed, this proved to be the case since the beneficial effects of red wine against AD were ascribed to resveratrol (Granzotto and Zatta, 2014) and several other polyphenolic compounds. Interestingly, a research carried out on 39 different red wine-related polyphenolic compounds, mainly quercetin, established their potent anti-amyloidogenic properties *in vitro* (Kim et al., 2005; Rigacci and Stefani, 2015 for review). A cohort study (Copenhagen City Heart Study) involving people with average age of 65

years and older, showed that monthly or weekly consumptions of red wine, but not other alcoholic drinks, reduce the risk of dementia including AD (Truelsen, Thudium, and Gronbaek, 2002). Another interesting prospective study, involving 3,777 participants and conducted for 3 years, revealed that drinking three to four glasses of red wine per day (250-500 ml/day) results in a four-fold reduced risk of dementia including AD when compared to subjects who drank less or non-drinkers (Orgogozo et al., 1997).

Although light-to-moderate alcohol consumption has been associated with a reduced risk of dementia and AD, extrapolating the benefic effects of red wine to alcohol consumption in general is still a matter of debate. The variability of the findings in the field are most likely due to possible interactions with other lifestyle-related (e.g., smoking) or genetic factors (e.g., apolipoprotein E gene variation). Indeed, protective effects of moderate alcohol consumption against cognitive decline are suggested to occur only in the absence of the AD-associated apolipoprotein E ε4 allele and where wine is the beverage (Panza et al., 2017).

Finally and needless to say, physicians/doctors should be cautious when advising patients regarding alcohol intake, given that excessive consumption can causes severe neurologic and other organ damages.

Olive oil

Several research findings suggest that diet rich in olive oil is associated with healthy aging and increased longevity (Vassallo and Scerri, 2013). MeDi recommends inclusion of 25 to 50 g/day of olive oil (Lopez-Miranda et al., 2010; Pitozzi et al., 2012; Qosa et al., 2015). The beneficial effects of olive oil are attributed, beside its high rates of polyunsaturated omega-3 fatty acids that is discussed in some following sections, to more than 30 phenolic compounds

able to inhibit Aβ and tau aggregation (Daccache et al., 2011; Monti et al., 2012; Abuznait et al., 2013; Grossi et al., 2013). Recent surveys and cohort studies have also suggested that olive leaf extract-based nutraceuticals protect against age-related degenerative diseases, diabetes, cardiovascular diseases and cancers (Covas, 2008; Psaltopoulou et al., 2011; Menotti and Puddu, 2013; Stefani and Rigacci, 2014). Recently, several studies have investigated the biochemical and biological effects of olive polyphenols, including oleuropein, hydroxytyrosol and oleocanthal. Indeed, plant polyphenols and their molecular scaffolds were considered as promising lead compounds for the development of new drugs that are specifically designed to combat many degenerative pathologies including aging-related neurodegeneration (Stefani and Rigacci, 2014; Rigacci and Stefani, 2015). Moreover, the olive oil polyphenol OLE (oleuropein aglycone) is known to inhibit the aggregation of the Aβ peptide, amylin and transthyretin at micromolar concentrations *in vitro* (Rigacci et al., 2010; Rigacci et al., 2011; Leri et al., 2016). In addition, oleuropein, OLE and hydroxytyrosol have been reported to hinder the *in vitro* aggregation of the tau protein into fibrillary tangles (Daccache et al., 2011). In addition, Kostomoiri et al. have established that OLE interacts in a non-covalent manner with the $A\beta_{40}$ peptide at a site spanning the Val12-Asn27 region, thereby reducing its aggregation propensity as confirmed by NMR analysis (Kostomoiri et al., 2013). OLE is also able to promote the α-secretase cleavage of the β-amyloid precursor protein (βAPP), thereby stimulating the non-amyloidogenic pathway and hence inhibiting the production of Aβ (Kostomoiri et al., 2013). Oleocanthal, another polyphenol present in olive oil, appears to increase Aβ clearance from the mouse brain through the up regulation of two important Aβ transporter proteins, LRP1 (Lipoprotein receptor-related protein 1) and p-glycoprotein, at the blood brain barrier (Abuznait et al., 2013). It also chemically alters the lysine residue K18 that is part of the fibrillogenic tau

hexapeptide VQIVYK sequence via Schiff base formation (Monti et al., 2011) and interacts with tau-441, thereby stabilizing the protein secondary structure and preventing its aggregation (Monti et al., 2012). Interestingly, OLE also protects against aggregated Aβ toxicity in transgenic mouse models of AD since its administration to the CL2600 strain of *C. elegans* constitutively expressing $A\beta_{3\text{-}42}$ results in a significant reduction of plaque deposits and oligomer in the muscle apparatus, with a significant decrease in severity of paralysis and an increase in worm life span (Diomede et al., 2013). Overall, due to their remarkable antioxidant potential, olive oil polyphenols interfere not only with the production, the aggregation and the clearance of Aβ, but also with tau fibrillogenesis and therefore undoubtedly stand as valuable anti-AD therapeutic factors.

Fish

Fish is a high-protein and low-fat food that provides a range of health benefits. White-fleshed fish, in particular, contains less fat than any other animal and oily fish contains high levels of polyunsaturated omega-3 fatty acids (omega-3 PUFA), the so-called "good" fats. Since the human body can't produce by itself enough amounts of these essential nutrients, fish is an important part of the diet. In addition, fish contains low amounts of the "bad" fats commonly found in red meat and called omega-6 fatty acids. Fatty acids are essential components of the central nervous system and are involved in brain development since they maintain the structural integrity of neuronal membranes (Panza et al., 2004; Arab and Sabbagh, 2010). It has been reported that consumption of fish twice a week results in a 60% reduction of the risk of developing AD (Morris et al., 2003a) and an epidemiological study revealed that fish consumption reduces the risk of developing dementia and aging-related diseases including AD

(Morris et al., 2003b). Another report showed that a regular intake of fish decreases the age-dependent cognitive decline and increases global cognitive functions (Otaegui-Arrazola et al., 2013).

As mentioned above, fish is known to contain high amounts of long chain-omega-3 PUFA (LC-n3-FA) such as eicosapentaenoic acid (EPA, C20:5, n-3) and docosahexaenoic acid (DHA, C22:6, n-3) (Otaegui-Arrazola et al., 2013). The richest source of DHA is fatty sea fish such as mackerel or salmon (Max Rubner-Institut, 2011) and it is established that LC-n3-FA is essential for growth and development of the infant brain during pregnancy and after birth (Kris-Etherton, Grieger, and Etherton, 2009). The principal LC-n3-FA, DHA, alone accounts for about 10-20% of total fatty acids of the brain and is fulfilling key roles during synaptogenesis, neuronal differentiation and synaptic function (McNamara and Carlson, 2006). It has also been proposed that DHA not only helps for brain development but also supports the maintenance of proper cognitive functioning in later life (Gomez-Pinilla, 2008). In this context, animal studies have established a significant improvement in learning and memory performance in rodents receiving supplementary DHA with their diet. Moreover, DHA might also convey beneficial effects under pathological conditions like AD. Indeed, it has been shown that DHA-enriched diet in aged mice significantly decreased total Aβ deposition by more than 70% when compared to low DHA control diet (Lim et al., 2005). These findings are consistent with several human epidemiological reports evidencing a correlation between the consumption of fish in general, and LC-n3-FA in particular, and higher cognitive performance as well as a reduced risk of developing dementia (Barberger-Gateau et al., 2005; McCann and Ames, 2005; Gomez-Pinilla, 2008; Fotuhi, Mohassel, and Yaffe, 2009). Moreover, these results have been confirmed in a large scale cohort

study with 6,158 participants in Chicago with average age of 65 years and older, in which fish consumption slows down age-dependent cognitive decline (Morris et al., 2005).

A recent report showed that, in mice, the fish oil-dependent increase of neuroprotection was due to D-1(NPD-1), an un-esterified DHA derivative (Afshordel et al., 2015). Although LC-n3-FA, mainly DHA, obviously exert protective effects on brain structure and cognitive functions, more large scale randomized clinical trials are needed before fish oil could be possibly recommended as a preventive therapeutic treatment against AD (Huhn et al., 2015). However, regarding fats in general, several previous works tend to indicate a significant impact of the consumption of this type of fat on the risk of developing AD.

Indeed, higher intake of PUFA might be helpful to AD (Boudrault, Bazinet, and Ma, 2009; Jicha, and Markesbery, 2010; Swanson, Block, and Mousa, 2012), since dietary supplementation with omega-3 PUFA affects the expression of genes involved in inflammatory processes (Vedin et al., 2012). However, this protective effect might be limited to APOE epsilon4 non carriers (Barberger-Gateau et al., 2013). Nevertheless, in a long-term 3.9 year follow-up cross sectional study, it has been shown that dietary intake of omega-3 PUFA as well as weekly consumption of fish lead to reduced onset of AD (Barberger-Gateau et al., 2002).

Importantly, an even larger prospective study with 1,449 participants and an average follow-up of 21 years. concluded that moderate consumption of saturated fatty acids was associated with an increased risk of AD and dementia, mainly among APOE epsilon4 carriers (Laitinen et al., 2006). In addition, a 1.5 year follow-up study in Singapore, showed that daily intake of omega-3 PUFA or fish was correlated with less age-dependent cognitive decline (Gao et al., 2011). However, in a prospective study with 482 women over a mean follow-up of 3 years and where a formalized food frequency was administered twice to know dietary consumption before

cognitive test, it appeared that a greater consumption of trans fat was not modifying cognitive decline (Naqvi et al., 2011). Finally, it has been shown that trans fatty acid consumption might augment odds of developing AD by promoting Aβ production via an increase of amyloidogenic and a decrease of non-amyloidogenic processing of βAPP (Grimm et al., 2012).

However, the systematic beneficial effects of unsaturated fatty acids need to be weighed against several observations (for review see Solfrizzi et al., 2010). Firstly, some population-based studies showed that although a higher monounsaturated fatty acids (MUFA) intake increased survival, high UFA/SFA ratio increased total mortality. Secondly, it has been evidenced that n-3 PUFA supplementation is efficient on cognitive symptoms only in very mild AD subgroups, MCI patients and cognitively unimpaired subjects non-APOE epsilon4 carriers. Altogether, these data support a putative beneficial role of UFA intake in maintaining proper cognitive function and possibly preventing cognitive decline and dementia at very early but not late stages of AD.

Fruits and vegetables

Regular intake of a medium to large amount of fruits is mainly associated with a reduced risk of developing AD and dementia (Smith and Blumenthal, 2010) and high consumption of vegetables appears to slow-down the rate of cognitive decline. These beneficial roles are most likely due to the presence of high amounts of antioxidants and bioactive vitamins as well as low levels of saturated fats (Smith and Blumenthal, 2010; Hu et al., 2013). Interestingly, high consumption of vegetables but not fruits was found to be associated with a reduced rate of cognitive decline in a clinical cohort study of 3,718 participants with an average of 65 years and older (Morris et al., 2006), with green leafy showing the strongest association. In another cohort

study of 2,613 participants between 43 and 70 years-old, high intake of vegetables such as cabbage, nuts and roots decreased the age-related cognitive impairment in middle aged individuals, with no significant changes in individuals consuming high amounts of fruits, legumes and juices (Nooyens et al., 2011).

Nevertheless, it has been recently reported that a daily supplementation with grape juice and wild blueberry juice for a period of 12 weeks improved learning and memory in individuals with memory decline (Vassallo and Scerri, 2013). Finally, in a Japanese-based population study involving a total of 1006 subjects followed for 15 years, characterized low rice diets, high intake of soybeans and its products, vegetables, or dairy products was associated with a reduced risk of developing AD (Ozawa et al., 2013).

After having presented the beneficial effects of some edible aliments, the following sections propose to focus on the anti-AD properties of the molecules present in the above described foods.

Polyphenols in diets and their impact on AD

Polyphenols are a class of small molecules that are composed of more than one aromatic phenol ring. Naturally occurring polyphenols are the most commonly found phytochemicals in consumable herbal beverages and foods worldwide (Joseph et al., 2007; Ramos, 2007). They constitute a large group of phytochemicals and more than 8000 natural polyphenol have already been identified in higher plants (Harborne and Williams, 2000). Natural polyphenols are categorized into several groups: vitamins (e.g., β-carotene and α-tocopherol), flavonoids (e.g., flavanone and isoflavone) and others (ellagic acid, sesamol, eugenol, etc.) and over the past few decades, polyphenols have been considered as protective candidates for the treatment of

neurological disorders (Weinreb et al., 2004; Bhullar and Rupasinghe, 2013). Polyphenols are plant secondary metabolites, which represent a large group of compounds with aromatic rings and hydroxyl groups with varied structural complexities. These groups of compounds exhibit wide range of activities such as free radical scavenging, chelation of transition metals and/or enhancing of endogenous antioxidant systems (Albarracin et al., 2012). For this reason, polyphenols were soon considered as possible neuroprotective factors.

There is an impressive number of plant-based extracts and their chemical constituents that have been shown to convey beneficial effects on human brain functions and a literature survey on this topic indeed generated some 30,000 articles, the vast majority of which being published during the last decade. Remarkably, epigallocatechin gallate (EGCG), resveratrol and curcumin contributed to over 15,000 of these publications. However, it has to be underlined here that only few of them have been assessed methodologically in human clinical trials. Overall, a handful of herbal extracts and their phytochemical components have garnered enough evidence in terms of improving brain function (Kennedy and Wightman, 2011).

Concerning AD, research carried out during the past decade has mainly focused on molecules able to interfere with amyloid aggregation and several plant polyphenols have been shown to display such properties. Turmeric (Curcuma longa), sometimes called "poor man's saffron", is the best known natural source of curcumin that is the most active constituent of turmeric. It has been reported that the compact and symmetric structure of curcumin is suitable for specifically bind to free Aβ peptides and inhibit their polymerization (Ono et al., 2004a). Curcumin was also shown to inhibit Aβ aggregation *in vitro* and to reduce amyloid load in transgenic mice (Yang et al., 2005) and curcumin amino acid conjugates can stimulate the α-secretase non amyloidogenic processing of βAPP (Narasingappa et al., 2012). Moreover, curcumin suppresses Aβ-induced

BACE-1 upregulation in human neuronal cells, attenuates the production of Aβ-induced ROS and prevents the formation of β-sheet rich secondary structures of Aβ (Shimmyo et al., 2008).

Another polyphenol, rosmarinic acid, was reported to inhibit Aβ-induced ROS formation, lipid peroxidation, DNA fragmentation and tau protein hyperphosphorylation (Iuvone et al., 2006). Rosmarinic acid is a phenolic compound mainly present in the genus of Labitae as well as in many other plants that exhibits several biological activities and is therefore traditionally used as an antioxidant and neuroprotective agent (Shekarchi et al., 2012).

Epigallocatechin galate (EGCG) is one of the natural polyphenol isolated from *Camellia sinensis* (green tea) that belongs to the Theaceae family. This plant is mainly found in hilly areas of China and India. Green tea has become a popular beverage across the world due to its beneficial effect on the brain (Gramza-Michalowska and Regula, 2007). This plant is known to contain many phenolics such as EC, ECG EGCG with EGCG being able to reduce the p75-ICD and JK2 pathway activation and noticeably to decrease the production of $A\beta_{1\text{-}40}$ and the expression of the amyloid precursor protein in the hippocampus of mice (Liu et al., 2014). EGCG also improves cognitive function in APP/PS1 transgenic mice by increasing the expression level of NGF and promoting CREB expression by c-Raf/ERK1/2-dependent TrkA phosphorylation (Liu et al., 2014). Moreover, EGCG reduces H_2O_2-induced apoptosis in PC12 cells by inducing neurite outgrowth through a PI3K/AKT/GSK-3β-mediated activation of caspase-3 and PARP cleavage (Koh et al., 2003). In addition, green tea potentiates the free radical scavenging system and activates CREB, BDNF, Bcl-2 protein, thereby most likely alleviating age-related neurodegeneration (Andrade and Assuncao, 2012). Of utmost interest is the fact that prolonged catechin treatment minimizes $A\beta_{1\text{-}42}$ production and enhances spatial

learning and memory (Li et al., 2009). Finally, it has been more recently demonstrated that EGCG inhibits $A\beta_{1-42}$ aggregation and fibril formation (Zhang et al., 2013).

Several polyphenols have the ability to scavenge ROS such as hydroxyl radicals, hypochlorous acid, peroxyl radicals and superoxide radicals (Halliwell, 2007). As a consequence, polyphenolic compounds isolated from fruits, vegetables, wine and tea have been shown to convey protection against oxidative stress and subsequent neuronal death (Schroeter et al., 2001). Polyphenols have thus been shown to increase the expression, in the hippocampus, of heat shock protein (HSP) 70 and insulin like growth factor 1 (IGF-1), which are responsible for protection against kainate-induced cell damage and supports learning and memory functions (Casadesus et al., 2004; Galli et al., 2006). Additionally, several animal studies have proven that polyphenols inhibit Aβ formation and clearance and alleviates cognitive deterioration (Hartman et al., 2006; Wang et al., 2006; Wang et al., 2008; Ho et al., 2009; Mori et al., 2012). Among other polyphenols with anti-AD properties, one can cite caffeic acid that is able to reduce the levels of intracellular calcium and tau phosphorylation (Sul et al., 2009). Very recently, it has been reported that α-mangostin can reduce Aβ production via the inhibition of β- and γ-secretase (Zhao et al., 2017). Finally, the olive polyphenol oleuropein aglycone protects against Aβ-induced toxicity in transgenic *C. elegans* model of AD (Diomede et al., 2013).

Now considering polyphenol-based clinical trials in humans, several interventional studies have been published so far. Data obtained from a randomized, double-blind clinical controlled trial with polyphenols supplementation in 100 subjects, have evidenced that polyphenols-containing antioxidant beverages trigger beneficial effects in AD patients by reducing homocysteine concentrations (Galasko et al., 2012). Regarding resveratrol, it has been shown that consumption of resveratrol (200 mg/day) in 23 subjects with an average age of 65 years

increases auditory, verbal and learning memory (Witte et al., 2014) and Kennedy and colleagues have established that the consumptions of 250 and 500 mg of resveratrol increase cerebral blood flow in the frontal cortex region of the brain, and that both doses also lead to a reduced concentrations of deoxy hemoglobin and increased oxygen uptake. These results showed that resveratrol has beneficial effect on normal human brain health but also in those suffering from diseases like AD and other neurological disorders (Kennedy et al., 2010). In addition, it has been reported that supplementation with high cocoa flavanol diet given to 50-69 years-old healthy participants, improves cognitive function when compared to placebo control (Mastroiacovo et al., 2015). Nontheless, Nurk et al. found, in a cross sectional study involving 2,031 subjects aged 70-74 years, that flavonol-rich foods such as wine, chocolate and tea, increase several cognitive abilities in a concentration dependent manner, when compared to non-consumer group over 1 year (Nurk et al., 2009). Finally, it has been evidenced, in a double-blind clinical trial, that consumption of pill-based nutraceuticals containing blueberry, green tea, vitamin D3, carnosine and biovalin, significantly increases processing speed of 52 subjects when compared to placebo (Small et al., 2014).

As far as curcumin is concerned, clinical oral trial with 4g/day of curcumin conducted with 27 AD patients for six months in a randomized, placebo-controlled, double-blind study was found to be safe and showed improvement in the patients (Baum et al., 2008; Belkacemi et al., 2011). Another interesting polyphenol-based clinical study demonstrated that soy isoflavone extracts, containing genistein, diadzein and glycetin have positive effects on mood and neurocognitive functions as well as on short and long term memory in males and females (File et al., 2005; Casini et al., 2006). Last but not least, the consumption of EGCG-rich green tea correlates with a reduced risk of developing neurodegenerative disorders and lowers the prevalence of cognitive

impairment (Weinreb et al., 2004; Nurk et al., 2009). Altogether, these results strongly suggest that consumption of plant polyphenols exerts beneficial effects on brain health and cognition in older humans and in AD patients. However, more studies are needed to clarify the effects of polyphenols on brain structure by using high resolution techniques such as MRI.

Vitamins in diet and their impact on AD

Vitamins (*vital amines*) are organic molecules that must absolutely be present in the diet because they cannot be synthesized in enough amounts by an organism. Vitamins and their metabolites are required for a large number of physiological processes. They have antioxidant properties and also regulate tissue growth and differentiation during embryonic development as well as calcium metabolism. (Rosenberg, 2007). The following statement by Albert Szent-Gyorgyi nicely describes the impact of vitamins on the body's vital organs, "A vitamin is a substance that makes you ill if you don't eat it." (Albert Szent-Gyorgyi, Nobel Prize in Physiology or Medicine, 1937). In the brain, vitamins and their metabolites are involved in many cellular processes including neuronal differentiation, neurotransmitter release, and long term potentiation and at the molecular level, they have the ability to regulate gene expression by interacting with many transcription factors (Lane and Bailey, 2005; Sodhi and Singh, 2014). Although the real impact of these molecules on AD is still not fully clarified, the following section summarizes our current knowledge on this topic.

Vitamin A

Vitamin A is a group of fat soluble retinoids found in dairy products, fish, liver, fortified cereals and the highest sources of provitamin A are carrots, broccoli and cantaloupe (Solomons, 2006). Vitamin A deficiency has been shown to cause cognitive dysfunctions and is a serious and widespread public health problem in developing countries. Vitamin A deficiency has also been linked to AD pathogenesis since decreased vitamin A levels were observed in AD patients (Rinaldi et al., 2003; Lopes da Silva et al., 2014), with significantly lower levels of vitamin A and β-carotene found in serum and plasma (Jimenez-Jimenez et al., 1999; Bourdel-Marchasson et al., 2001; Rinaldi et al., 2003). In a recent study, Aβ production was shown to be increased in the brain parenchyma of hypovitaminosis mouse model while sAPPα content is lowered, thereby indicating a shift from the non-amyloidogenic to the amyloidogenic processing of βAPP (Reinhardt et al., 2016).

Moreover, vitamin A and β-carotene are supposed to play key roles in the prevention and treatment of AD, considering their ability to attenuate the formation of Aβ oligomers and fibrils (Ono and Yamada, 2012). Indeed, a vigorous decrease in cerebral Aβ accumulation together with improved cognitive functions was observed under supplementation with trans-retinoic acid over eight weeks in a transgenic mouse model of AD (Ding et al., 2008). Similar results on cognition and Aβ load have been obtained in streptozotocin-induced demented mice in which supplementation with trans-retinoic acid reduces oxidative stress, restores AChE activity and decreases myeloperoxidase levels (Sodhi and Singh, 2013). In line with this, treatment of APP/tau-double transgenic mice with a RARα (retinoic acid receptor α) agonist leads to a decrease of Aβ load and improves cognitive performances while an activation of the Aβ-degrading enzymes neprilysin (NEP) and insulin degrading enzyme (IDE) has been established in microglia after activation of RARα signaling (Reinhardt et al., 2016).

A very recent study has also evidenced that marginal vitamin A deficiency (MVAD) stimulates β-site APP cleaving enzyme (BACE1), promotes the production of Aβ and the formation of neurotic plaque, thereby ultimately impairing memory in experimental AD mouse model and that supplementation with a therapeutic dose of vitamin A reverses the MVAD-induced memory deficits (Zeng et al., 2017). Finally, vitamin A and β-carotene were shown to have anti-amyloidogenic potential by inhibiting Aβ oligomerization and altering the stability of preformed Aβ fibrils *in vitro*, most probably through their binding to the C-terminal region of the peptide (Ono et al., 2004b; Takasaki et al., 2011).

Vitamin D

Vitamin D is a fat soluble vitamin that is quite different from other vitamins due to the fact that our body can synthesize most of vitamin D by exposure to sunlight. Vitamin D acts as a pro-hormone and controls hormone balance and immune regulation of the body. The pro-vitamin D is largely found in fish, ham, pork chops, chicken, fortified milk, cheese, fortified soy milk, fortified orange juice and fortified breakfast cereals. Vitamin D is an important organic molecule for normal physiological functions and protection of the central nervous system (CNS) and the vitamin D3 subtype has been established as an anti-ischemic, anti-oxidative and anti-inflammatory factor (Gu et al., 2012). As far as AD is concerned, it has been recently reported that deficits in vitamin D could promote neurodegeneration (Gezen-Ak, Yilmazer, and Dursun, 2014; Annweiler et al., 2015; Landel et al., 2016) while individuals with dementia or AD display lower circulating concentrations of 25-hydroxyvitamin D (Balion et al., 2012; Annweiler, Llewellyn, and Beauchet, 2013). Very recently, Banerjee and colleagues showed that altered

levels of vitamin D and pro-inflammatory cytokines in serum leads to AD and depression (Banerjee et al., 2017).

The association between vitamin D and AD was further strengthened by the identification of many vitamin D receptor polymorphisms as AD susceptibility factors (Gezen-Ak et al., 2007; Lehmann et al., 2011; Wang et al., 2012; Lee, Kim, and Song, 2014). Nonetheless, some clinical trials have established a beneficial effect of vitamin D supplementation in AD patients. Firstly, Annweiler et al. showed that vitamin D3 supplementation, together with memantine treatment, improves the cognitive functions and memory in patients with moderate AD (Annweiler et al., 2011). This result indicates a probable synergistic effect of memantine plus vitamin D, as shown by the greater reduction of Aβ-induced axonal degeneration in the presence of both compounds when compared with monotherapies (Annweiler et al., 2014). Secondly, a study carried out with 1,604 men has evidenced an association between low 25-hydroxyvitamin D level and cognitive dysfunction (Slinin et al., 2010).

Importantly, vitamin D is involved in several cellular mechanisms that are modified in AD pathogenesis, including Aβ production, Aβ clearance, enzymatic degradation of Aβ peptides and tau phosphorylation (Keeney and Butterfield, 2015). Thus, supplementation with vitamin D3-enriched diets decreases the burden of Aβ in brain and improves cognitive functions in rodents (Yu et al., 2011; Briones and Darwish, 2012; Durk et al., 2014) while an increase of both $A\beta_{40}$ and $A\beta_{42}$ levels has been established in brain tissue of vitamin D-deficient animals (Wang et al., 2012; Grimm et al., 2014).

Worth mentioning is the study by Wang and colleagues showing that 1α,25-(OH)2D3 inhibits βAPP promoter transactivation in human neuroblastoma SH-SY5Y cells, thereby indicating that the observed reduction of Aβ secretion in the presence of vitamin D could be due, at least partly,

to a decreased gene expression of its precursor (Wang et al., 2012). In addition, vitamin D might also inhibit tau phosphorylation as recently described by Cheng et al. (Cheng et al., 2016). Another recent study also revealed that vitamin D2 blocks the phosphorylation of NF-κB in $A\beta_{25-35}$-treated BV2 microglial cells and attenuates oxidative stress by decreasing ROS generation and the production of inflammatory cytokines (Raha et al., 2016).

Finally and very recently, Feart et al. evidenced, in a prospective cohort study of 916 French participants aged 65 years and older, that vitamin D deficiency correlates with an increased cognitive decline and a three fold increased risk of developing AD (Feart et al. 2017).

Vitamin E

Vitamin E is a lipid-soluble antioxidant present in a variety of foods such as vegetable oils and fats, seeds and nuts. Several animal and non-interventional studies have reported that vitamin E might convey a protective role against AD (Farina et al., 2017) and studies involving aged healthy adults have detected an association between low levels of vitamin E and impaired cognitive functions (Perrig, Perrig, and Stahelin, 1997; Cherubini et al., 2005). Moreover, Mangialasche et al. reported lower levels of both forms of vitamin E (tocotrienols and tocopherols) in the plasma of individuals with AD and myocardial infarction (Mangialasche et al., 2012). In addition, antioxidants, including vitamin E, were found to improve cognitive performance of aged rodents (Socci, Crandall, and Arendash, 1995) and vitamin E supplementation leads to decreased levels of cerebral Aβ in young, but not in aged transgenic mice (Sung et al., 2004). More recent investigations have reported that dietary supplementation with α-tocopherol, α-lipoic acid and N-acetylcysteine inhibits age-related alterations in Aβ metabolism in rat brains and improves learning and memory functions (Thakurta et al., 2014)

and similar effects have been observed with oral supplementation of α-tocopherol quinine, an oxidative metabolite of α-tocopherol that ameliorates memory impairment, as shown by a reduced level of cerebral Aβ oligomers, decreased oxidative stress and a lower production of inflammatory mediators in APP/PS1 double transgenic mice (Sinha et al., 2016). Moreover, supplementation with vitamin E in tau transgenic mice results in delayed/suppressed development of tau pathology together with an improved health and a decreased of motor disabilities (Nakashima et al., 2004) and tau-induced neurodegeneration in drosophila is reversed when flies are treated with vitamin E (Dias-Santagata et al., 2007).

It has also been very recently proved that tocotrienol inhibits the formation of Aβ oligomers and fibrils in a dose-dependent manner and attenuates Aβ pathology in βAPP_{swe}/PS1ΔE9 double transgenic mice (Ibrahim et al., 2017). In addition α-, γ-, and δ-tocopherol were found to inhibit the transcription of β- and γ-secretases and to increase Aβ degradation in SH-SY5Y neuroblastoma cells (Grimm et al., 2015). On a clinical point of view, the consumption of vitamin E has been associated with decreased odds of developing AD. Firstly, Morris et al. have evidenced that there is a decreased AD risk only when vitamin E is consumed from foods, not from supplement (Morris et al., 2002). However, in a double-blind randomized study conducted with 769 subjects, no significant differences in the probability of developing AD was observed in the vitamin E group when compared to placebo controls (Kang et al., 2006). In the meantime, Zandi and colleagues carried out cross-sectional and prospective study of 4740 demented patients 65 years of age or older. The authors concluded that supplements of vitamin C and E in combination are associated with a reduced incidence of AD (Zandi et al., 2004). Finally, a recent report carried out with 7540 individuals aged 60 and over has established that supplementation with the antioxidants vitamin E (400 IU/day) and selenium (200 μg/day) did not forestall/prevent

dementia and are not recommended as anti-AD preventive agents (Kryscio et al., 2017), thus leaving a doubt as to the use of vitamin E as a therapeutic tool against AD.

Vitamin K

Vitamin K is a group of fat-soluble vitamins that are essential for the human body to complete the synthesis of several proteins involved in blood coagulation and in controlling the binding of calcium in bones and tissues (DiNicolantonio, Bhutani, and O'Keefe, 2015). Vitamin K is largely found in green vegetables and olive oil but is also present in eggs, chicken and butter. In the brain, vitamin K predominantly occurs as vitamin K2 (menaquione-4), which participates to cellular growth, mitogenesis, myelination, chemotaxis and neuroprotection (Ferland, 2012). Studies related to vitamin K and its effect on behavior and cognition are very limited in humans although vitamin K concentration in serum has been reported to be decreased in AD patients (Sato et al., 2005a; Shatenstein, Kergoat, and Reid, 2007; Presse et al., 2008). For instance, Presse and colleagues conducted a detailed analysis of the intake of phylloiquinone in 31 community-dwelling early-stage AD patients when compared with 31 age- and sex-matched controls and showed that mean phylloquinone consumption was considerably lower in patients (Presse et al., 2008). Because green vegetables, fruits and fats contribute to more than 70% of total phylloquinone intake, a lower consumption of green vegetables by AD patients may account for their overall lower vitamin K levels (Presse et al., 2008). Moreover, a study performed with community-dwelling subjects involving 100 women with AD and 100 age-matched controls, found that plasma phylloquinone levels were significantly lower in AD

patients when compared to controls and that serum levels positively correlate with cognition based on Mini-Mental State Examination (MMSE) and negatively correlates with uncarboxylated form of the vitamin K-dependent proteins (VKDP) osteocalcin (Sato et al., 2005b). The number of vitamin K-related animal studies is also very limited, although it has been shown that vitamin K-deficient diet significantly reduces the locomotor activity in aged rats (Cocchetto et al., 1985) and that low-phylloquinone diet accentuates cognitive deficit in aged, but not in young rats (Carrie et al., 2011).

In vitro studies also reported that vitamin K3 analogs can inhibit Aβ aggregation and protect neuroblastoma cells from Aβ-induced toxicity, thereby suggesting that vitamin K may exert protective effects against AD through anti-amyloidogenic properties (Huy et al., 2013), a hypothesis recently reinforced by Alam and colleagues who showed that vitamin K3 is able to inhibit $A\beta_{42}$ aggregation and fibrillogenesis (Alam et al., 2016).

Interestingly, vitamin K is also involved in brain sphingolipid metabolism by inducing serine palmitoyl-CoA transferase (SPT) and cerebroside sulfotransferase. The biosynthesis of sphingolipid is carried out by condensation of pamitoyl CoA and L-serine to 3-ketosphinganin, to form ceramide. Cerebroside sulfotransferase is one of the enzymes involved in the conversion of ceramide into sulfatides. Therefore, vitamin K deficiency leads to a reduction of cerebral sulfated levels in rodents, a lack that is overcome by vitamin K supplementation in animals (Sundaram and Lev, 1988; Sundaram et al., 1996). In this context, it is not surprising that sulfatides levels are decreased in the brain, cerebrospinal fluid and plasma of AD patients (Han et al., 2002; Han et al., 2003; Cheng et al., 2013; Gonzalez de San Roman et al., 2017). Moreover, sulfatides were shown to decrease Aβ peptides levels through the facilitation of apolipoprotein-mediated clearance of Aβ in cultured cells (Zeng and Han, 2008).

B-complex vitamins

B vitamins are a class of water-soluble vitamins that play important roles in cell metabolism. Rich sources of B vitamins include legumes, whole grains, banana, potato, nutritional yeast, chili peppers and molasses (Winklera et al., 2006). B vitamins such as B1, B2, B6, niacin (B3), folate (B9) and B12 have been associated with protection against cognitive decline and AD (Morris, Schneider, and Tangney, 2006) most likely by inhibiting oxidative stress and reducing the concentration of homocysteine (Hashim et al., 2011, Nilforooshan et al., 2011). As a consequence, a non-negligible amount of clinical studies have been conducted during the past years. Firstly, a large meta-analysis study, involving 2,835 subjects and 9 folic acid supplements together with placebo, evidenced that folic acid with or without other B vitamins had no significant effect on cognitive function within 3 years after starting treatment (Wald, Kasturiratne, and Simmonds, 2010). Secondly, a randomized controlled study with 140 subjects with mild to moderate AD was performed in which the effect of vitamin B consumption on homocysteine levels and cognitive functions was assessed. Individuals were assigned to take 1mg of methycobalamin and 5mg of folic acid daily for 2 years. The results established that, although homocystein amounts were reduced, there was no particular group difference in any of the neuropsychological scores (Kwok et al., 2011). Thirdly, 271 individuals over 70 year old with mild cognitive impairment received high doses of B vitamins containing 0.8mg of folic acid, 0.5mg of cyanocobalamin (vitamin B12) and 20mg of pyridoxine hydrochloride (vitamin B6). After two years follow-up, those who had received the vitamin-B regimen suffered significantly less brain shrinkage (atrophy) compared to those who had received a placebo, as measured by volumetric MRI scans (Smith et al., 2010) and another supporting study measured

lower levels of vitamin B12 in individuals with increased chances of developing AD or dementia (Wang et al., 2001). Hooshmand and colleagues showed, in 271 samples of Finnish-community people 65-79 years of age, that those who were administered vitamin B12-rich food were less prone to develop AD in later years (Hooshmand et al., 2010). In addition, it has been reported that vitamin B12, folate and thiamin levels were lower in people with severe dementia of Alzheimer's type when compared to age-matched controls (Renvall et al., 1989). Moreover, an eight year follow-up study from the U.S. Ramingham trial found that 25% of adults are deficient in vitamin B12 and that nearly half the population has suboptimal vitamin B12 blood levels (Tangney et al., 2011a). Therefore, it is important to be conscious of this matter of fact and correct it, as people with high levels of indicators of vitamin B12 deficiency display lower performance on cognitive tests, more brain shrinkage and smaller brain total volume (Tangney et al., 2011a). Interestingly, Corrada et al. described decreased odds of developing AD with vitamin B6 consumption (Corrada et al., 2005). Another study found that dietary intake of niacin (vitamin B3) provides protection against AD, since individuals receiving the highest intake of niacin had an 80% reduction in AD risk (Morris et al., 2004).

In a cohort study of 816 subjects, it has been shown that folate deficiency induces an increased risk of developing AD (Ravaglia et al., 2005) and that a folate-rich diet reduces this risk (Corrada et al., 2005, Luchsinger et al., 2007). Moreover, humans with low vitamin B12 have high rate of cognitive decline, even if they display high folate levels or consumed folate supplements. Indeed, poor Mini-Mental Status Examination was correlated to low vitamin B12 and B6 but not folate or homocysteine levels (Moorthy et al., 2012). However, in a recent report by Zhang et al., it has been evidenced that folic acid along with B vitamin supplement in AD patient showed a significant reduction in homocyteine levels when compared to control patients

(Zhang et al., 2017). Thus, based on the existing data, one can reasonably state that reducing homocysteine levels leads to an improvement of cognitive performance and reduces the risk of developing AD (Zhang et al., 2017). Finally, Kobe and colleagues showed in a cross-sectional study with 100 MCI patients aged 50-80 years that low-normal vitamine B12 levels associated with significantly poorer learning abilities and recognition performance and that the microstructure integrity of the hippocampus was altered in these individuals (Kobe et al., 2016).

Interestingly, multi-vitamin supplementation with vitamin B6/B12/folate+choline can considerably suppress hypoxia-induced memory deficits in mice, mainly through a decrease in homocysteine concentrations in serum, and markedly attenuates tau hyperphosphorylation via the inhibition of GSK-3β (Yu et al., 2016). In a very recent study by Alam et al. vitamin B12 was shown to inhibit $A\beta_{42}$ aggregation and amyloid-induced toxicity in a dose dependent manner in a human neuronal cell line (Alam et al., 2017).

A comprehensive anti-Alzheimer's lifestyle

Overall, it seems obvious that, although there is no clear cut life styles that can accurately cure existing AD and considering the fact that there exists no efficient anti-AD treatment so far, some proper preventive good habits can undoubtedly minimize the risk of developing the disease. This includes, for a large part but not exclusively, nutrition. Indeed, diet composed of food having minimal amounts of saturated fatty acids is advised, while consuming foods having high rates of polyunsaturated fatty acid, polyphenols and vitamins would certainly help reducing the risk of developing AD.

Nutrients that have been proved beneficial to postpone the onset of AD obviously need to be recommended for consumption. Alzheimer’s disease is a major public health concern for

patients, care givers and patient families not only as a financial burden but also because it is physically and mentally demanding. One preventive way to combat AD could be the intake of appropriate diet containing molecules able to protect neurons from AD-related insults. In this context, foods like fish, fruits and vegetables, via the action of some of their components such as polyphenols, polyunsaturated fatty acids and vitamins, were shown to be protective via their antioxidant, anti-neuroinflammatory and anti-amyloidogenic activities. From the *in vitro, in vivo* and clinical studies extensively reviewed here, there is no doubt that diet has a non-negligible impact on alleviating, minimizing or even preventing the neurodegenerative processes occurring in AD. Thus, MeDi has been globally recognized as one of the healthiest dietary pattern in the world and it has a strong potential in maintaining brain health and slowing down cognitive impairments. Altogether, epidemiological studies have reported that consumption of antioxidants, vitamins, polyunsaturated fatty acids, fruits and vegetables, dairy products, as well as moderate amounts of red wine reduces the risk of developing AD. This regular, mild and safe preventive anti-AD approach should receive our attention in the near future.

Conclusion

Overall the current review summarizes the relation between diet and AD. An increasingly accepted notion is that nutritional compounds exert neuroprotective and neurorescue effects not only through antioxidant activities but also via combined abilities to minimize amyloid load, decrease mitochondrial dysfunction, suppress neuroinflammation and modulate signaling pathways. Numerous extensive *in vitro* and *in vivo* experimental evidences have shown that nutrients such as vitamins, polyphenols and polyunsaturated fatty acids, which are present in

fruits, vegetables, red wine and fish, have strong potential to alleviate and/or attenuate the neurodegenerative process in AD.

Adherence to the Mediterranean diet has been reported to reduce the risk of AD. However, very few studies that have been done suggest that higher intake of fruits, vegetables, fish, nuts, legumes, cereal, lower intake of meats, high fat diary, sodium, sweets, and refined grains could be associated with reduced risk of AD.

Thus, further studies are now needed to definitely link the consumption of nutrients, foods and dietary patterns to a reduced risk of developing AD. Additionally, randomized experimental designs are needed to explore a causal link between AD and dietary choices and such studies should explore changes in dietary choices over time. Ultimately, the success of clinical trial will determine the relevance of dietary nutrients to be incorporated as key components in clinical practice to modulate the onset and/or progression of AD.

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Conflict of interest

Authors have no conflict of interest.

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Legends to figures

Figure 1: Overview of the risk and protective factors having an impact on the development of Alzheimer's disease. On one hand, both intrinsic (diabetes, obesity, hypertension, ApoE polymorphism and rare genes mutations) and extrinsic (heavy intake of alcohol, smoking, unhealthy diet, head injury) factors that amplify the deleterious intrinsic status, clearly represent a risk to develop AD. On the other hand, proper modifications of the life style such as balanced diet (including MeDi), regular physical activity, sustained societal interactions and brain exercise) have been shown to exert protective actions.

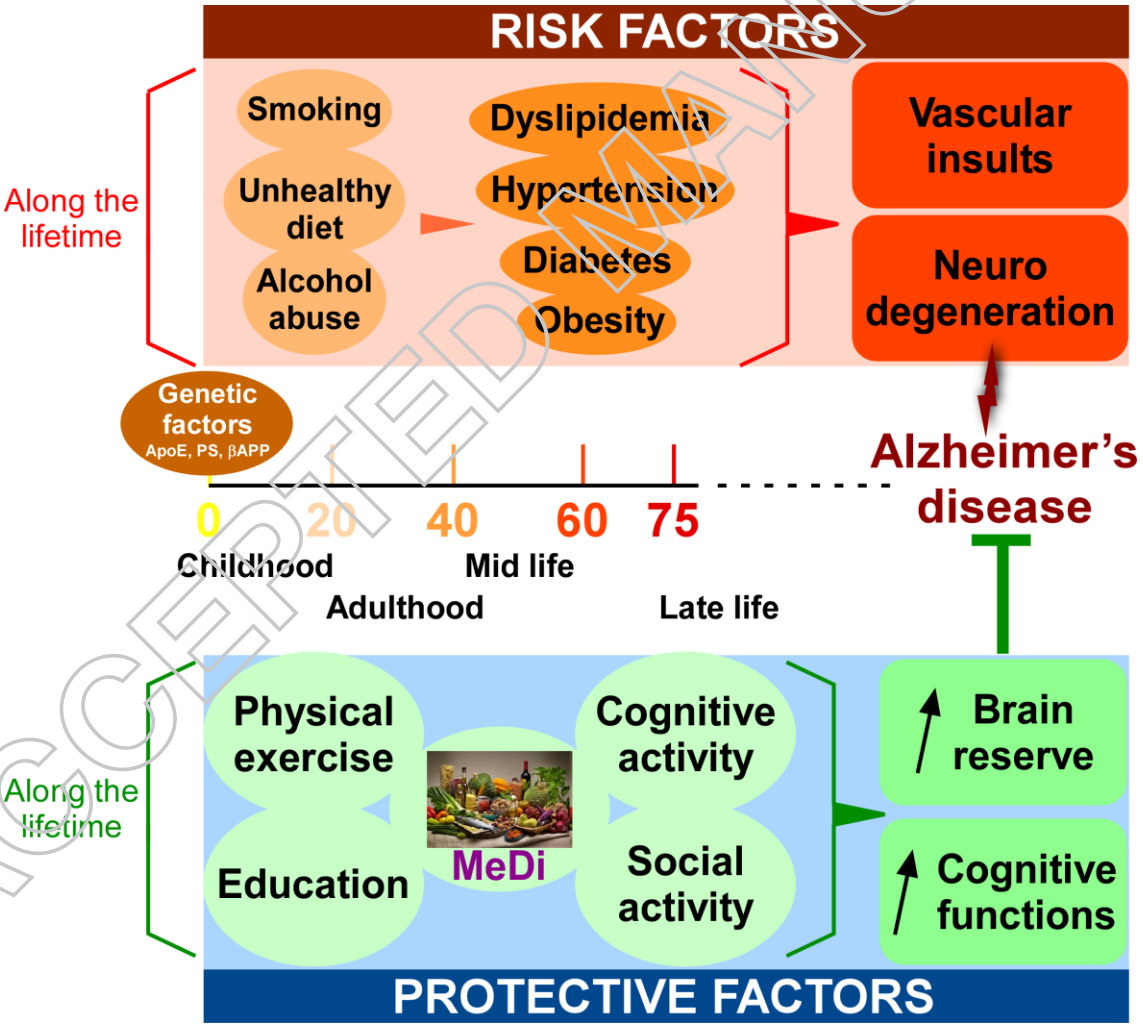


Figure 2: Diet-dependent modulation of oxidative stress. Oxidative stress is mainly involved in the development and progression of many neurodegenerative diseases. A number of events including excitotoxicity, mitochondrial dysfunction, $Ca2^{+}$ overload and endoplasmic reticulum stress are associated with excess accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leading to oxidation of proteins, lipids and DNA. Continuous exposure of ROS/RNS leads to the activation of antioxidant enzymes and repair systems and alters the function of transcription factors and kinases, thereby modulating the expression of various genes. Some modifications of gene transcription may also be mediated by cytokines released in response to ROS/RNS. In this context, the antioxidant and scavenging activities of neuro-nutrients such as phytochemicals, vitamins, hormones and neurotrophic factors limits the extent of neurodegenerative disease progression by alleviating oxidative stress.

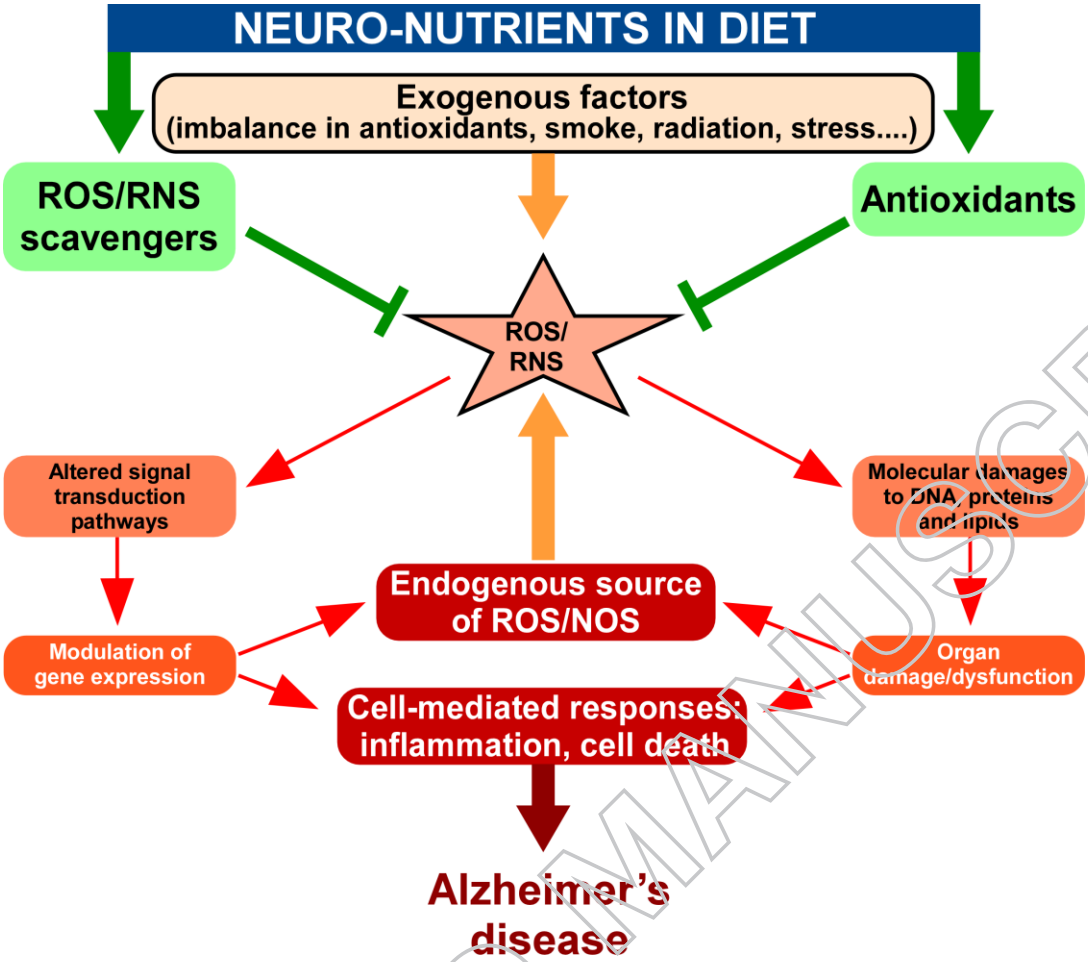
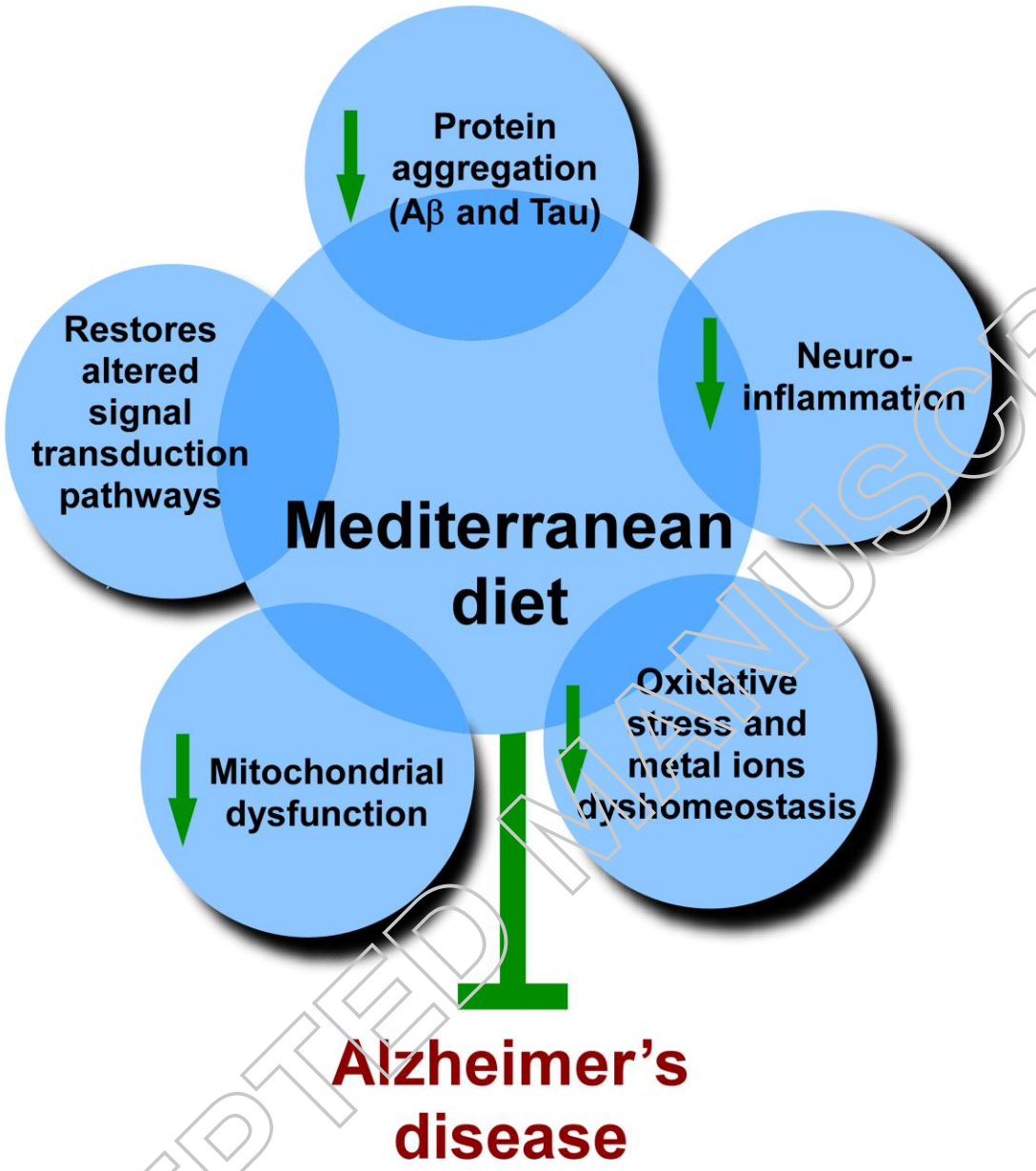


Figure 3: Mediterranean diet and Alzheimer's disease. Alzheimer's disease (AD) is a complex neurodegenerative disorder with multiple contributing factors. Among the many processes that lead to neurodegeneration in AD, one can cite amyloid aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction and the alteration of some signaling pathways. Components of the Mediterranean diet interact with all these factors or processes, thereby possibly preventing or delaying the onset of AD.



ble 1

aracteristics of human studies using Mediterranean (MeDi) or MeDi-related diets (references are listed in chronological ascendi
er)

e of y	Cohort	Country	Age	Diet	Follow-up	Food measure	Key findings	Reference
pective	4,615	Canada	65	Wine Coffee	5 years	Self report	Associates with a reduced risk of developing AD	Lindsay et al., 2002
pective	815	USA	65-94	Fish, n-3 Fatty acids	3.9 years	Harvard FFQ	People consuming fish once per week or more have less risk (60%) of developing AD	Morris et al., 2003b
pective	980	USA	65+	Wine (3 daily serving)	up to 4 years	SFFQ	Modest to moderate wine intake may be associated with a lower risk of developing AD	Luchsinger et al., 2004
pective	5,201	USA	65+	Fatty fish	0.1 to 8.4 years	NCI FFQ	Associates with a reduced risk of dementia (28%) and AD (41%)	Huang et al., 2005
pective	1,836	USA	65+	Fruit and vege-table juices (3 times/week)	9 years	CASI	Delay the onset of AD (less effect in ApoE4 allele carriers and not physically active people	Dai et al., 2006
e	1,984	USA	65+	MeDi	1.8-11.9	SFFQ	Higher adherence to MeDi correlates with	Scarmeas et al.,

rol					years		reduced onset of AD	2006a
pective	2,258	USA	65+	MeDi	0.2-13.9 years	SFFQ	Higher adherence to MeDi correlates with reduced onset of AD	Scarmeas et al., 2006b
pective	8,085	France	65+	Fruits, fish, vegetables, omega-3 rich oils	4 years	BFFQ	Decrease the risk of dementia and AD, especially among ApoE4 non-carriers	Barberger-Gateau et al., 2007
pective	192	USA	65+	MeDi	0.2-13.6 years	SFFQ	High adherence to MeDi correlates with lower risk of mortality	Luchsinger et al., 2007
ulation-d	1,409	Finland	65-79	Coffee (3-5 cups/ day or >5 cups/day)	21 years	20 item test	The lowest risk (65% decrease) is found in people who drank 3-5 cups/day	Eskelinen et al., 2009
pective	1,410	France	65+	MeDi	5 years	FFQ	High adherence to MeDi correlates with slower cognitive decline (MMSE)	Feart et al., 2009
s onal	2,031	Norway	70-74	Chocolate (10g/day + wine (75-100ml/day)	2 years	FFQ KOLT TMT-A m-DST	Flavonoid- rich foods dose-dependently increase cognitive performance (MMSE)	Nurk et al., 2009
pective	282	USA	65+	MeDi	0.9-16.4 years	SFFQ	High adherence to MeDi associates with reduced risk of conversion of MCI to AD	Scarmeas et al., 2009

pective	1,219	USA	65+	MeDi	up to 3.9 years	SFFQ	High adherence to MeDi correlates with an average of 34% lower risk of developing AD. Introduction of inflammatory and metabolic markers does not change the degree of association	Gu et al., 2010
s onal	2,031	Norway	70-74	Carrots, cruciferous vegetables, citrus fruits)	2 years	FFQ KOLT TMT-A m-DST	Dose-dependently improve cognitive abilities (MMSE)	Nurk et al., 2010

ble 1 (continued)

pective	3,790	USA	65+	MeDi	7.6 years	FFQ	High adherence to MeDi correlates with slower cognitive decline. After alteration of several variables, no difference was observed with the HEI-2005	Tangney et al., 2011
s- onal	970	Australia	60+	MeDi	18 months	CCVFFQ	MeDi adherence was found considerably different between healthy CT and AD and between healthy CT and MCI when assessing MMSE	Gardener et al., 2012
pective	1,006	Japan	60-79	Soybeans, vegetables,	15 years	SFFQ	Associates with a reduced risk of developing dementia	Ozawa et al., 2013

				algae, milk, dairy products, low rice				
pective	16,058	USA	70	MeDi	6 years	Self report	MeDi adherence correlates with improved cognition	Samieri et al., 2013
s onal	45	USA	54±11	MeDi + physical activity	up to 4 years	SFFQ	Lower physical activity+MeDi associates with higher brain AD burden when compared with higher physical activity+MeDi	Matthews et al., 2014
s onal	52	USA	54±12	MeDi	-	SFFQ PET	Low adherence to MeDi correlates with cortical thinning of AD-affected brain regions when compared to high adherence to MeDi	Mosconi et al., 2014
s onal	52	USA	54±12	NP1, NP2 NP3, NP4, NP5	-	Harvard/ Hill FFQ	NP1-4 prevent from AD by modulating AD-risk through an effect on Aβ and associated neuronal impairment, whereas NP5 promotes AD	Berti et al., 2015
ospective	819	USA	75+	Fish oil	5 years	Self report	Associates with less atrophy in several brain regions	Daiello et al., 2015
pective	175	USA	59+	Fruits	11.6 years	-	Consuming 2/3 fruits/day and >3 fruits/ day are associated with lower risk for developing AD (40% and 61% respectively) when compared with < 1 fruit/day	Williams, 2015

previations: **NP1**, nutritional pattern: B-vitamins (B1, B2, B3, B6, B9); **NP2**, nutritional pattern: mono and polyunsaturated f
3, nutritional pattern: vitamin A, carotenoids, vitamin C, dietary fibers; **NP4**, nutritional pattern: vitamin B12, vitamin D, zi
5, nutritional pattern: saturated, trans-saturated fats, cholesterol, sodium; **MMSE**, Mini Mental Status Exam **HEI-2005**, Heal
ing Index–2005; **FFQ**, Food Frequency Questionnaire; **NPE**, Neuropsychological evaluation. **CCVFFQ**, Cancer Council of Victo
d Frequency Questionnaire; **SFFQ,** Semi quantitative Food Frequency Questionnaire; **KOLT**, Kendrick Object Learning T
T-A, Trail Making Test, part A; **m-DST**, modified version of Digit Symbol test. **BFFQ**, Brief Food Frequency Questionnaire. **N**
tional Cancer Institute. **CASI,** Cognitive Abilities Screening Instrument; **PET**, positron emission tomography

ble 2

aracteristics of anti-AD properties of molecules present in the foods (references are listed in chronological ascending order)

e of y	Cohort	Country	Age	Diet/levels	Follow-up	Key findings	Reference
pective	633	USA	65+	Vitamin C and vitamin E supplements	4.3 years	High doses of vitamin C and vitamin E supplements may lower the risk of developing AD	Morris et al., 1998
pective	5,395	Netherland	67+	Vitamin C (54.1 mg/day) + vitamin E (6.2 mg/day)	6 years	High dietary intake of vitamin C and vitamin E may lower the risk of developing AD	Engelhart et al., 2002
pective	815	USA	65+	Niacin	6 years	High food intake of niacin may protect against AD and age-related cognitive decline	Morris et al., 2004
domized s over	22	England	21-29	Resveratrol (250 and 500 mg/day twice)	45 min	Dose-dependently increases cerebral blood flow	Kennedy et al., 2010
pective	232	Sweden	80+	Vitamin E levels (blood)	6 years	Vitamin E high levels associates with a reduced risk of developing AD at advanced age	Mangialasche et al., 2010

domized rolled	156	England	76-77	Daily B-vitamins (folic acid, 0.8 mg, vitamin B6, 20 mg, vitamin B12, 0.5 mg)	2 years	Slows the atrophy of specific brain regions and lowers homocysteine levels	Douaud et al., 2013
pective	1,658	USA	73.6	Vitamin D levels (serum)	5.6 years	Vitamin D deficiency associates with an increased risk of developing dementia and AD	Littlejohns et al., 2014
s onal	49	USA	25-72	Vitamin B12 Vitamin D Folate ω-3 PUFA β-carotene	1 year	Associates with lower Aβ load in AD regions and reduced glucose metabolism	Mosconi et al., 2014
domized rolled	52	USA	65-85	Pill-based neutraceutical (NT-020)	2 months	Improves the cognitive abilities of older adults	Small et al., 2014
rventional	23	Germany	50-75	Resveratrol (200 mg/day)	26 weeks	Associates with better verbal episodic memory performance and improved glucose metabolism	Witte et al., 2014
rventional	40	Germany	50-80	Resveratrol (200 mg/day)	26 weeks	Reduces glycated hemoglobin, preserves hippocampus volume and improves hippocampus RSFC in at-risk patients for dementia	Kobe et al., 2017

previations: **AD**, Alzheimer's disease; **RSFC,** Resting-State Functional Connectivity; **ω-3 PUFA**, omega-3 Poly-Unsaturated Fa
d.