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The Effects and Mechanisms of Phytochemicals on Alzheimer's Disease Neuropathology

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by

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A Project submitted in partial satisfaction of
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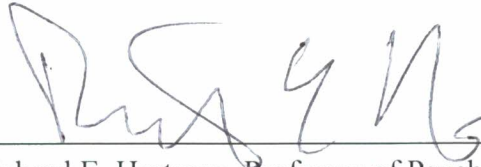
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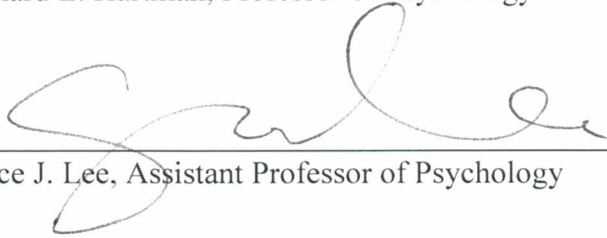
Each person whose signature appears below certifies that this project in his/her opinion is adequate, in scope and quality, as a project for the degree Doctor of Psychology.

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CONTENT

ABBREVIATIONS

Aβ	Amyloid Beta
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
BBB	Blood Brain Barrier
CREB	cAMP response element binding protein
EGCG	epigallocatechin-3-gallate
NFT	neurofibrillary tangle
sAPPα	soluble APP-α
SAC	s-allyl cysteine

ABSTRACT OF THE DOCTORAL PROJECT

The Effects and Mechanisms of Phytochemicals on Alzheimer's Disease Neuropathology

by

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Doctor of Psychology, Graduate Program in Psychology
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Dr. Richard E Hartman, Chairperson

Alzheimer's disease effects millions of people, yet pharmacological treatments are limited. In the absence of effective treatments, identifying factors that can decrease the risk of developing Alzheimer's disease is of significant interest. A growing body of epidemiological and experimental evidence suggests that dietary fruits and vegetables can have neuroprotective effects against the harmful effects of oxidative stress, neuroinflammation, and aging. These effects are mediated by various phytochemicals, which are compounds found in plants that can possess antioxidant, anti-inflammatory, and other beneficial properties. This review addresses epidemiological and experimental evidence for the effects and potential mechanisms of several commonly consumed phytochemicals on Alzheimer's disease neuropathology and outcomes. The data suggest that regular consumption of bioactive phytochemicals from a variety of fruits and vegetables attenuates age- and insult-related Alzheimer's disease neuropathology.

CHAPTER ONE

INTRODUCTION

Phytochemicals are compounds produced by plants, some of which (e.g., phenols, terpenes, and organosulfurs) result in pigmentation, odors, and irritants that can protect the plant from internal (e.g., metabolic) insults like protein overexpression and free radical reactive oxygen species (ROS), and external (e.g., environmental) insults like predators, pathogens, ultraviolet radiation, and other threats to the plants' survival. Consumption of plants that produce these phytochemicals seems to produce health benefits for humans mediated by modulating several biological pathways, including inflammatory processes, neuronal cell death (apoptosis), neurogenesis, neurotransmission, and enzyme function (Rossi, Mazzitelli, Arciello, Capo, & Rotilio, 2008; M. Singh, Arseneault, Sanderson, Murthy, & Ramassamy, 2008). Many of these pathways have a direct effect on the development of Alzheimer's disease (AD) and other types of age-related neuropathology. This review will provide a brief overview of AD etiology, followed by an outline of dietary phytochemicals that have been shown to affect age- and AD-related neuropathology and functional outcomes.

CHAPTER TWO

ALZHEIMER'S DISEASE NEUROPATHOLOGY

Recent prevalence rates suggest that over 5 million Americans currently have AD (Alzheimer's Association, 2014), which is behaviorally characterized by a presentation of memory, motor, language, and executive dysfunction. The neuropathological markers of AD were originally thought to be limited to the formation of amyloid plaques surrounding neurons and the presence of neurofibrillary tangles (NFTs) of tau protein inside neurons. However, in recent years, the significance of mitochondrial dysfunction, neuroinflammation, astrogliosis, microglial activation, synaptic loss, neuronal damage, apoptosis, disruption of blood brain barrier (BBB) permeability, bacterial and viral infections, and intestinal microbiota have all been identified as significant contributors to AD neuropathology (Alonso et al., 2014; Bayer & Wirths, 2010; Block & Hong, 2005; Borgesius et al., 2011; Bredesen, 2009; Cherry, Olschowka, & O'Banion, 2014; Devi & Anandatheerthavarada, 2010; Houlden et al., 2016; Moreira, Carvalho, Zhu, Smith, & Perry, 2010; Rubio-Perez & Morillas-Ruiz, 2012; Schindowski, Leutner, Kressmann, Eckert, & Müller, 2001; Soscia et al., 2010; Terwel et al., 2011; Xue, Sparks, & Streit, 2007; Yao et al., 2004; Zlokovic, 2008).

Plaque accumulation has been identified in the medial temporal lobe, particularly the hippocampus and entorhinal cortex, prior to the emergence of behavioral symptoms. These structures have been implicated in learning and memory processes, which explains the cognitive impairments associated with AD. The extracellular plaques consist mainly of amyloid-beta (Aβ) peptides cleaved from larger amyloid precursor proteins (APP) by γ-secretase and β-secretase enzymes. The increasing concentration of extracellular Aβ

monomers gradually results in their polymerization into diffuse aggregates and eventually dense-core amyloid plaques (Wirths, Multhaup, & Bayer, 2004). Other proteins (e.g., apolipoproteins) and non-proteins (e.g., metals, hemes, and ROS) have also been found within the plaques (Dong et al., 2003; Mohsenzadegan & Mirshafiey, 2012; Roher, Palmer, Yurewicz, Ball, & Greenberg, 1993; Rosen et al., 2016). An age related increase in cortical and subcortical amyloid plaque levels is one of the most salient AD biomarkers (Victor L. Villemagne et al., 2011). NFTs, another prevalent AD biomarker, are damaged tau-based microtubules that disrupt intracellular transport mechanisms. Typically, these damaged neurons are found in areas with higher Aβ concentrations. Eventually, these damaged neurons are unable to function properly, leading to neuronal death. One current hypothesis for the etiology of AD is that the gradual accumulation of Aβ between the neurons initiates inflammatory and oxidative processes that lead to the formation of synaptic loss, NFTs, and neurodegeneration, particularly in neurons that use acetylcholine and glutamate (Palop & Mucke, 2010; Selkoe, 2002; Wirths et al., 2004).

Aβ neurotoxicity has been demonstrated in hippocampal cell cultures (Reifert, Hartung-Cranston, & Feinstein, 2011), and the deleterious effects of Aβ deposition on synaptic functioning in the brain have been demonstrated using long-term potentiation (LTP), an in vitro model of learning and memory (Kimura, MacTavish, Yang, Westaway, & Jhamandas, 2012; Shipton et al., 2011; Walsh et al., 2002). Aβ has also been shown to induce hypersensitivity to excitotoxicity (i.e., damage caused by dysfunctional firing of glutamate) and oxidative stress in vitro (Matos, Augusto, Oliveira, & Agostinho, 2008; Nakayama et al., 2011). Furthermore, the formation of Aβ-heme peroxidase complexes within Aβ plaques begins a neuroinflammatory cascade leading to release of ROS and

damage to muscarinic acetylcholine receptors within the brain (Atamna, Frey, & Ko, 2009; Fawcett et al., 2002). Importantly, these damaging effects can be ameliorated by dietary antioxidants (Kiko et al., 2012; Ono, Hamaguchi, Naiki, & Yamada, 2006; Peake, Suzuki, & Coombes, 2007). Although the accumulation of extracellular Aβ plaques is a prominent feature of the AD brain, synaptic loss within and surrounding the plaques may be a better predictor of the cognitive dysfunction seen in AD than the total amount of Aβ plaque deposition (Giannakopoulos et al., 2003; Schmitz et al., 2004). Individuals may be biologically more or less susceptible to neuronal buildup of Aβ, which may explain why the overall Aβ plaque burden is generally not a direct indicator of AD symptom severity (Tosun et al., 2011; V L Villemagne et al., 2013).

Although it is currently unclear whether Aβ deposition is a primary cause of the neurodegeneration and behavioral deficits associated with AD, the gradual accumulation of Aβ in the brain appears to be associated with progressive oxidative stress and various harmful downstream effects. Oxidative stress associated with AD is believed to be partly responsible for damage to neuronal structures that contributes to functional deficits and ultimately neuronal death. Furthermore, experimental evidence suggests that manipulating levels of Aβ deposition in the brain can influence the emergence of behavioral deficits.

For example, accelerated Aβ plaque accumulation tends to increase the risk of developing behavioral deficits associated with AD (i.e., learning and memory problems). Pathophysiological conditions that accelerate Aβ accumulation in the brain have been shown to increase the risk of developing AD. These conditions include Down syndrome, which is characterized by an overproduction of APP in the brain, leading to elevated Aβ

production and deposition. Individuals with Down syndrome are typically diagnosed with some form of dementia by approximately 50 years of age (Head et al., 2001; Netzer et al., 2010; Schupf et al., 2007). Additionally, several inheritable mutations in the genes for APP or γ-secretase lead to elevated APP production and Aβ deposition in the brain and an earlier onset of AD (Bird, 2008; Cacace, Sleegers, & Van Broeckhoven, 2016; Krüger, Moilanen, Majamaa, & Remes, 2012). Identification of these genes has resulted in the development of transgenic rodent models of AD that express high levels of human APP and develop age-related neuropathology and cognitive deficits congruent with Aβ aggregation and deposition in the brain (Cohen et al., 2013; Hochgräfe, Sydow, & Mandelkow, 2013; Kitazawa, Medeiros, & M. LaFerla, 2012; Morrissette, Parachikova, Green, & LaFerla, 2009). Transgenic rodent models of AD focused on Aβ plaque development appear to mirror the behavioral hallmarks of AD seen in humans diagnosed with AD (Richard E. Hartman, Lee, Zipfel, & Wozniak, 2005). Additionally, in vivo imaging shows that Aβ plaques can aggregate rapidly in transgenic rodent brains, and that markers of neurodegeneration around these Aβ plaques develop quickly (Meyer-Luehmann et al., 2008; Yan et al., 2009). Finally, neuroinflammatory processes and oxidative stress can induce accumulation of APP and Aβ in the brain, increasing the risk for developing AD. Common sources of these insults include traumatic brain injury, stroke, chronic low-level hypoxia (e.g., due to breathing problems), the "Western" diet (Abdul-Muneer, Chandra, & Haorah, 2015; Beer, Blacker, Hankey, & Puddey, 2011; Candore et al., 2010; Chamorro, Dirnagl, Urra, & Planas, 2016; Fernández-García, Cardona, & Tinahones, 2013; Iturriaga, Moya, & Del Rio, 2015; Jelic & Le Jemtel, 2008; Pistell et al., 2010; Pradeep, Diya, Shashikumar, & Rajanikant, 2012; Stranahan, Cutler,

Button, Telljohann, & Mattson, 2011; Q.-G. Zhang et al., 2012), and (importantly) the accumulation of Aβ. Oxidative stress is a common component of all brain injury and can induce further Aβ accumulation, initiating a harmful cycle of progressive oxidative and inflammatory load in the brain (Castellano et al., 2011; Jofre-Monseny, Minihane, & Rimbach, 2008).

In addition to the observation that accelerating Aβ accumulation can increase the risk of developing AD and associated behavioral deficits, experiments with transgenic rodent models of Aβ plaque accumulation in the brain have shown that reducing Aβ levels in the brain can improve behavioral outcomes. These experiments include systemic treatments with monoclonal anti-Aβ antibodies and dietary manipulations that prevent, or in some cases reverse, the neuropathology and behavioral deficits associated with AD (Bernardo et al., 2009; Demattos et al., 2012; Richard E. Hartman, Lee, et al., 2005; Richard E Hartman et al., 2006; Joseph, Cole, Head, & Ingram, 2009; E. B. Lee et al., 2006; Mark, 2010; Patten, Moller, Graham, Gil-Mohapel, & Christie, 2013; Pop et al., 2010; Steele, Stuchbury, & Münch, 2007; A. Wang, Das, Switzer, Golde, & Jankowsky, 2011; J. Wang et al., 2005). Reducing oxidative load in the brain is another pathway to improving cognitive function in Aβ transgenic rodent models without reducing Aβ levels (Kotilinek et al., 2008; Ongali et al., 2014; Tong, Lecrux, & Hamel, 2012). These findings suggest that Aβ contributes to the process of oxidative stress overload that gradually impacts the function of brain structures that mediate learning and memory.

In summary, AD is associated with an abnormal buildup of Aβ plaques in the brain, which ultimately induces even greater Aβ accumulation in the brain. This "amyloid cascade" process creates a damaging cycle of neurodegenerative decline, including the

formation of NFTs, synaptic dysfunction and loss, excitotoxicity and apoptosis (A.

Armstrong, 2014; Barage & Sonawane, 2015; Musiek & Holtzman, 2015; Pimplikar,

2009). Current pharmacological approaches for treating AD have focused on stabilizing

glutamatergic activity by blocking NMDA channels (e.g., memantine) and inhibiting

acetylcholinesterase (AChE), an enzyme that breaks down acetylcholine and has been

shown to induce $A\beta$ aggregation (e.g., galantamine, tacrine, donepezil, and rivastigmine).

NMDA antagonists can slightly slow the progression of AD symptoms and may reduce

the susceptibility of neurons to excitotoxic degeneration. AChE inhibitors have been

shown in animal experiments to slow AChE's promotion of $A\beta$ aggregation.

Nevertheless, pharmacological treatments that target glutamate and acetylcholine have

ultimately yielded disappointing results. Other experimental approaches that have yielded

mixed results. Active and passive $A\beta$ immunotherapies in transgenic mouse models of

AD have yielded promising results, even in the absence of significant reductions in $A\beta$

burden (Buttini et al., 2005; Richard E Hartman, Izumi, et al., 2005; Wilcock et al.,

2004). Human immunotherapy treatment has been more problematic, due to significant

toxicity and tolerability concerns (Gilman et al., 2005; Lemere, Maier, Jiang, Peng, &

Seabrook, 2006; Mangialasche, Solomon, Winblad, Mecocci, & Kivipelto, 2010; Schenk,

Hagen, & Seubert, 2004; Siemers et al., 2010; Winblad et al., 2012). Although theses

pharmacological failures have raised questions about the amyloid cascade hypothesis of

AD, it has also been proposed that $A\beta$ may initiate a multi-faceted pathogenic cascade

that causes AD, rather than acting as the sole causative factor (A. Armstrong, 2014;

Imtiaz, Tolppanen, Kivipelto, & Soininen, 2014; Salomone & Caraci, 2012). These

downstream processes include tau aggregation, extracellular senile plaque formations,

mitochondrial dysfunction, neuroinflammatory processes, blood brain barrier (BBB) permeability disruption, and gut microbiome disturbances (Biron, Dickstein, Gopaul, Jefferies, & Hendey, 2011; Devi & Anandatheerthavarada, 2010; Hedskog et al., 2013; Miao et al., 2016; Moreira et al., 2010; Musiek & Holtzman, 2016; Narasingapa et al., 2012; Rom et al., 2016; V. Singh et al., 2016; T. Yuan et al., 2016). Despite the lack of significant progress towards effective pharmacological interventions for AD, mounting epidemiological and experimental evidence indicates that diet and other sources of bioactive phytochemicals can significantly decrease the risk of developing AD neuropathology and symptoms by several potential mechanisms (Barnard et al., 2014; R E Hartman, 2009; Kang et al., 2014; Lau, Shukitt-Hale, & Joseph, 2005).

CHAPTER THREE

PHYTOCHEMICALS AND ALZHEIMER'S DISEASE

A growing body of literature demonstrates that several bioactive phytochemical compounds, including vitamins (e.g. tocopherols and folic acid) and other organic compounds (e.g. phenols, terpenes, and organosulfurs) can affect aspects of the AD disease process. Potential mechanisms for these effects include antioxidant / anti-inflammatory properties and modulation of Aβ concentrations and toxicity. Indeed, several pharmacological interventions of interest in AD stem from traditional herbal medicines. For example, the AChE inhibitor galantamine is derived from daffodil plants, and the anti-inflammation drug aspirin is derived from salicylic acid, a polyphenol found in the bark of willow trees. Both phytochemicals have garnered interest in the treatment of AD. Additionally, the role of the gut microbiome has been of increasing interest in studying the activity and mechanisms of dietary phytochemical compounds. Approximately 100 trillion diverse species of very metabolically active bacteria line the intestinal tract and have a strong influence (both pro- and anti-) on neuroinflammation, neuromodulation, and neurotransmission in the brain and periphery. The role of the potentially neurotoxic and proinflammatory microbial activations and their relationship to age-related amyloidogenesis and neurodegeneration are of increasing interest (Petra et al., 2015; Y Zhao, Dua, & Lukiw, 2015). In addition to the gut's role in the disease process of AD, its microbiome is also highly implicated in the bioavailability and bioactivation of dietary phytochemicals. It has been shown that 5-10% of dietary phytochemicals are absorbed initially. The remaining phytochemicals reach the colon, where they undergo extensive metabolizing by microbiota. Although the metabolic pathways and the

molecular targets are not well understood, the intestinal microbiome's breakdown of dietary polyphenols may enhance their beneficial properties (H. Chen & Sang, 2014; Chiou et al., 2014; Gasperotti et al., 2015; Marín, Miguélez, Villar, & Lombó, 2015; Parkar, Trower, & Stevenson, 2013). Recent studies of the pharmacokinetic activity of several microbiome-produced polyphenol metabolites found that many of them reached the brain in statistically significant concentrations (Gasperotti et al., 2015; D. Wang et al., 2015; T. Yuan et al., 2016). The following sections provide a survey of the epidemiological and experimental evidence for the effects of various plants, phytochemicals, and their metabolites on AD processes.

Epidemiological Evidence

Several studies have demonstrated that regular consumption of a variety of fruits and vegetables can decrease the risk for developing AD and slow its progression. For example, a large Swedish study collected dietary questionnaires from young adults approximately 40 years before regular cognitive screenings began in older age. It was found that higher fruit and vegetable consumption in earlier life was associated with a decreased risk of dementia and AD (Hughes et al., 2010). Similarly, a study of Irish adults, aged 64-93 years, found that consuming more fruits and vegetables was associated with significantly better overall cognitive functioning (Power et al., 2015). However, another study reported that consumption of dietary tocopherols (isoforms of vitamin E), vitamin C, P-carotene, and tea were not correlated with the risk of developing AD (Dai, Borenstein, Wu, Jackson, & Larson, 2006).

Additionally, epidemiological evidence that isolated phytochemicals can affect

AD remains elusive. A study of older American adults to identify dementia incidence and AD diagnoses found that the use of vitamins C and E alone or in combination did not reduce AD or dementia incidence after a 5-year follow-up (Gray et al., 2008). Another study examining the effects of vitamin E supplementation in mild cognitive impairment (MCI) and AD found no evidence that it was beneficial (Farina, Isaac, Clark, Rusted, & Tabet, 2012). However, one study of older Chinese adults reported that lower α-tocopherol levels were found in those diagnosed with MCI than in healthy controls (L. Yuan et al., 2016), and another recent study found that higher dietary intake of vitamins A, C, and E is associated with protection from AD (Berti et al., 2015). Nevertheless, the evidence suggests that acquiring vitamins through a varied diet of vitamin rich foods may provide more protection from AD than the use of vitamin supplementation. A recent study of elderly French adults examined the association between dietary vitamin B consumption and long-term incidence of dementia. Higher intake of dietary vitamin B reduced the risk of dementia with an approximately 50% lower risk for individuals consuming the highest amounts compared to the lowest consumers (Lefèvre-Arbogast et al., 2016).

Furthermore, growing epidemiological evidence suggests that dietary omega-3 fatty acids, most commonly found in flax, nuts, algae, and oil from fish that eat algae, may protect against developing AD (Burkholder-Cooley, Rajaram, Haddad, Fraser, & Jaceldo-Siegl, 2016; Perim Baldo et al., 2016; Robertson et al., 2016; Song et al., 2016; Tavakkoli-Kakhki et al., 2014). The so-called "Mediterranean" diet, which is characterized by regular consumption of foods with high fatty acid content from fish, nuts, and oils, has been of increasing interest, due to the growing body of evidence that it

is associated with several health benefits, including a reduced incidence of AD.

Consumption of dietary fatty acids appears to explain a portion of the diet's

neuroprotective characteristics (Trichopoulou et al., 2014), and several epidemiological

studies have demonstrated that diets supplemented with olive oil and/or nuts are

associated with improved cognitive function in older adults (Perim Baldo et al., 2016;

Sjögren et al., 2010; Valls-Pedret et al., 2015).

Other sources of bioactive phytochemicals include colorful, flavorful, and

aromatic spices. These spices often contain high concentrations of various phenols,

terpenes, and organosulfurs. For example, a study of elderly adults showed that those

whose diets included curry performed significantly better on neuropsychological tests of

cognitive performance (Ng et al., 2006). This spice mix includes turmeric, a bright

yellow root that contains a high concentration of the polyphenol curcumin. Light to

moderate wine consumption has also been associated with a reduced risk for AD,

although it remains unclear whether the effect is due to grape polyphenols (e.g.,

resveratrol) or ethanol (which itself is derived from plants) (Arntzen, Schirmer,

Wilsgaard, & Mathiesen, 2010; Covas, Gambert, Fitó, & de la Torre, 2010; Orgogozo et

al., 1997).

Phytochemicals can also be consumed by other methods other than diet. For

example, smoking tobacco was previously thought to possibly offer protection from Aβ

deposition and the occurrence of AD. This was in large part due to postmortem

examinations of the brains of AD that showed significantly lower levels of Aβ in the

entorhinal cortex of smokers (Court et al., 2005). However, recent epidemiological

studies have identified smoking as a risk factor for the development of AD (Norton,

Matthews, Barnes, Yaffe, & Brayne, 2014). A large community study of adults in the US found that older individuals who currently smoke are more likely to develop AD than those who never smoked. Given that experimental evidence of nicotine administered in animal models of AD suggests that nicotine may be neuroprotective (see section on nicotine), it appears likely that the act of smoking tobacco, rather than consumption of nicotine itself, increases the risk for developing AD, despite evidence of decreased postmortem $A\beta$ in smoker's brains.

In summary, epidemiological evidence suggests that consuming a wide variety of fruits and vegetables that contain high concentrations of bioactive phytochemical compounds may work collectively and synergistically to lower the risk for developing AD. Relatively few experimental clinical trials have been published assessing the effects of plant/phytochemical consumption on AD in humans. Several experimental preclinical studies using transgenic animals and/or in vitro models have provided evidence that various aspects of AD neuropathology can be manipulated by plants and their phytochemicals. The following subsections outline recent experimental literature describing the varied potential benefits of bioactive phytochemicals on AD neuropathology.

Experimental Evidence

Polyphenols

Many plants produce polyphenols (large assemblies of phenols, which are molecules that contain an aromatic ring bonded to a hydroxyl group). These include common phytochemicals like the phenolic acids, stilbenoids, and flavonoids.

Phenolic Acids

Several phenolic acids have been shown to modulate neuropathological pathways related to AD. For example, rosmarinic acid (derived from rosemary) and nordihydroguaiaretic acid (derived from creosote) have been shown to prevent and reverse Aβ aggregation in vitro (Farr et al., 2016; Lucarini et al., 2013; Rahman, Ansari, Rehman, Parvez, & Raisuddin, 2011). Additionally, coffee and tea are plants with relatively high concentrations of phenolic acids that possess antioxidant and anti-inflammatory properties, such as caffeic acid and various tannins (Brezová, Šlebodová, & Staško, 2009; Esquivel & Jiménez, 2012; Ludwig et al., 2012; Vignoli, Bassoli, & Benassi, 2011). Coffee and tea are also discussed in the section on psychoactive alkaloids (caffeine), and tea is discussed in more detail in the section on flavonoids (flavans).

Diets containing high amounts of the spice mixture curry have been associated with improved cognitive performance in elderly individuals (Braskie et al., 2011; Ng et al., 2006). Curcumin is a phenolic acid found in the curry spice turmeric, which is a bright yellow root related to ginger. It is structurally similar to thioflavine-S and Congo red, which are histological stains used to visualize amyloid fibrils in brain tissue. Interestingly, curcumin will also bind to amyloid fibrils in brain tissue sections and can be visualized under a fluorescent microscope to observe Aβ plaques (Reinke & Gestwicki, 2007; Ringman, Frautschy, Cole, Masterman, & Cummings, 2005). In addition to its Aβ binding properties in tissue sections, it has also been demonstrated to prevent and reverse Aβ aggregation in vitro (Ono, Hasegawa, Naiki, & Yamada, 2004; Yang et al., 2005).

Experimentally, dietary curcumin has been reported to prevent oxidative stress,

synaptic damage, cortical microgliosis, and learning deficits in rats after

intracerebroventricular infusion of Aβ (Frautschy et al., 2001). It also decreased Aβ

plaques and oxidative stress in APP transgenic mice (G. P. Lim et al., 2001; Ono et al.,

2004; Yang et al., 2005) and reduced heme-Aβ peroxidase damage to muscarinic ACh

receptors (Atamna et al., 2009). More recent studies with both rats and mice have

examined whether curcumin attenuates inflammation and mitochondrial dysfunction in

models of neurological insult. The results suggested that curcumin reduced post-insult

lesion sizes and inflammatory biomarkers in the brain, and improved mitochondrial

function and behavioral outcomes (Laird et al., 2010; Miao et al., 2016). Additionally, a

transgenic mouse study demonstrated increased levels of DNA damage relative to control

mice, and reported that dietary supplementation with curcumin significantly reduced the

damage (Thomas et al., 2009). Its experimental effects are not limited to rodent models.

A recent drosophila (fruit fly) experiment found that curcumin reduced oxidative stress

and protected against age-related neurodegeneration (Seong et al., 2015), and a study of

elderly humans after 12 weeks of curcumin supplementation demonstrated improved

artery endothelial function by increased vascular nitric oxide bioavailability, reduced

overall oxidative stress, and improved conduit artery endothelial function (Parker et al.,

2016). Curcumin also inhibits the pro-inflammatory cytokine nuclear transcription factor-

κβ (NF-κβ) (B. B. Aggarwal & Shishodia, 2004) and modulates other cell-signaling

pathways (B. B. Aggarwal & Shishodia, 2006). Curcumin also possesses potent

antimicrobial properties which may possibly have direct or indirect effects on Aβ

aggregation or other neuropathological pathways to AD. An In vitro study of curcumin

demonstrated that curcumin dose-dependently inhibits the formation of Aβ fibrils and

destabilizes already formed Aβ fibrils. However, the mechanism by which Curcumin inhibits Aβ fibril formation and Aβ fibril destabilization remains unclear and could be due to a synergistic effect of curcumin's anti-aging and anti-microbial properties (Kumaraswamy, Sethuraman, & Krishnan, 2013; Ono et al., 2004; Rai, Singh, Roy, & Panda, 2008).

The anti-amyloid and antioxidant activity of curcumin has generated great interest for the treatment of AD. However, the insolubility of curcumin in water has restricted its use. This restriction may be overcome by the synthesis of curcumin nanoparticles that maintain anti-oxidative properties, are non-cytotoxic, and can destroy amyloid aggregates, thus approaching the treatment of Alzheimer's disease from several angles.

Pomegranates have been consumed as food and used medicinally for millennia and contain high concentrations of punicalagins, which break down in water to smaller phenolic acids such as ellagic acid, ellagitannins, and gallic acid (Ambigaipalan, De Camargo, & Shahidi, 2016; Elfalleh et al., 2011; Heber, 2011; Johanningsmeier & Harris, 2011; Larrosa et al., 2010; Legua et al., 2012; Masci et al., 2016; Sreekumar, Sithul, Muraleedharan, Azeez, & Sreeharshan, 2014; Venkata, Prakash, & Prakash, 2011; R. Wang, Ding, Liu, Xiang, & Du, 2010). Several animal and human studies have shown that pomegranate juice and extracts demonstrate significant bioactive properties, including antioxidant and anti-inflammatory effects (Al-Kuraishy & Al-Gareeb, 2016; M. Aviram et al., 2000; Michael Aviram et al., 2004; BenSaad, Kim, Quah, Kim, & Shahimi, 2017; Bishayee et al., 2011, 2013; Cano-Lamadrid et al., 2016; de Nigris et al., 2005; Husari et al., 2016; Kaplan et al., 2001; Larrosa et al., 2010; Matthaiou et al., 2014; Mertens-Talcott, Jilma-Stohlawetz, Rios, Hingorani, & Derendorf, 2006; Rosenblat,

Volkova, Coleman, & Aviram, 2006; Rozenberg, Howell, & Aviram, 2006; Seeram et al., 2005). Pomegranate juice, extracts, and their bioactive constituents suppress inflammatory cell signaling, reduce expression of oxidation-sensitive genes and pro-inflammatory cytokines in response to cellular stress, reduce blood biomarkers of inflammation and oxidative stress, and modulate endothelial nitric oxide synthase expression (Adams et al., 2006; L. G. Chen, Liu, Hsieh, Liao, & Wung, 2008; Ghavipour et al., 2016).

Animal experiments in which rodents have been given pomegranate extracts or had pomegranate juiced added to their drinking water have demonstrated the neuroprotective effects of the pomegranate's bioactive phytochemicals. The amount of juice consumed was similar, on a mg/kg basis, to a human dose of 1 to 2 cups of pure pomegranate juice. Initially, pomegranate's neuroprotective propertied were demonstrated when the offspring of pomegranate-supplemented pregnant mice were protected from neonatal hypoxic-ischemic brain injury (Loren, Seeram, Schulman, & Holtzman, 2005). These results prompted experiments with APP transgenic mice, in which 6 months of consumption reduced Aβ plaques in the hippocampus and improved maze performance (Richard E Hartman et al., 2006). Later experiments suggested that the reduction in Aβ levels likely resulted from modulations in APP enzymatic processing, presumably leading to less production of Aβ and increased production of soluble APP-α (sAPPα, an endogenous neuroprotective peptide produced by α-secretase processing of APP). Another study showed that ellagic acid derived from pomegranate rinds inhibited β-secretase activity in vitro (Kwak et al., 2005). More recent mouse studies examining the consumption of pomegranate peel extract showed increased brain-derived

neurotrophic factor expression and reduced Aβ plaque density, AChE activity, lipid peroxidation, and pro-inflammatory cytokine expression (Morzelle et al., 2016). These results were similar to other APP transgenic mouse studies in which pomegranate juice supplementation improved learning and memory and reduced Aβ plaque deposition (Rojanathammanee, Puig, & Combs, 2013) and showed significant improvements in memory, learning, and locomotor function while reducing anxiety (Subash et al., 2015). Another recent mouse study showed that pomegranate supplementation protected against proton irradiation-induced anxiety (Dulcich & Hartman, 2013). Finally, pomegranate supplementation has been experimentally demonstrated to improve cognitive performance in humans after heart surgery (Ropacki, Patel, & Hartman, 2013) and with mild cognitive impairment (Bookheimer et al., 2013).

Overall, this growing body of experimental evidence shows that the phenolic acids found in pomegranates may directly or indirectly provide significant behavioral and neuropathological protection against age-related disorders, including AD, by multiple mechanisms that work together to prevent establishment and progression of Aβ deposition and neurodegeneration. Interestingly, in vitro experiments show that isolated phytochemical components may not provide as much benefit as the whole juice, suggesting that the wide variety of phenolic acid isoforms present in the whole fruit may provide synergistic benefits (Seeram et al., 2005). One study even showed that the conjugated sucroses, fructoses, and glucoses found in pomegranates also have antioxidant properties (Rozenberg et al., 2006). Some recent studies have shown that bacteria in the gut can metabolize the large punicalagins into smaller anti-inflammatory molecules like urolithin-A that may have higher bioavailability (Espín, Larrosa, García-Conesa, &

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Tomás-Barberán, 2013; Larrosa et al., 2010; Seeram et al., 2006; T. Yuan et al., 2016). These findings suggest that further comparative studies of isolated phytochemical metabolites may lead to increased understanding of their true mechanisms of action and the mediating role of microbiome metabolism. Finally, numerous other studies have shown pomegranate and its bioactive constituents to be anti-carcinogenic, antibacterial, anti-apoptotic, and protective for the cardiovascular system (Ahmed, El Morsy, & Ahmed, 2014; Al-Kuraishy & Al-Gareeb, 2016; M. Aviram et al., 2000; Michael Aviram et al., 2004; Braga et al., 2005; K. Cao et al., 2015; Chavez-Valdez, Martin, & Northington, 2012; de Nigris et al., 2005; Howell & Souza, 2013; Kaplan et al., 2001; Riaz & Khan, 2016; Rosenblat et al., 2006; Rozenberg et al., 2006; Seeram et al., 2005; Shafik & El Batsh, 2016; Syed, Chamcheu, Adhami, & Mukhtar, 2013; L. Wang, Li, Lin, Garcia, & Mulholland, 2013), suggesting that consumption of pomegranates and their juice may protect against AD neuropathology and a several other age-related disease processes.

Stilbenoids

Resveratrol is a stilbenoid polyphenol found in grapes and nuts that has been shown to induce Aβ clearance and decrease Aβ levels in vivo in part via intracellular proteasome-facilitated degradation of Aβ (Karuppagounder et al., 2009). Additionally, resveratrol modulates several Aβ-related cell-signaling pathways (Capiralla et al., 2012; Köbe et al., 2017; Porquet et al., 2014), which may explain the epidemiological evidence for a decreased risk of developing AD among elderly individuals who drink small to moderate amounts of wine. Experimental models of traumatic brain injury have

demonstrated that treatment with resveratrol immediately after traumatic brain injury

reduces oxidative stress and even reduces lesion volume (Ates et al., 2007). These

findings are supported by resveratrol's neuroprotective effects in adult and neonatal

rodent models of ischemic stroke (Wan et al., 2016; West, Atzeva, & Holtzman, 2007).

Flavonoids

The flavonoid class of polyphenols includes the flavans and pigment compounds like the

anthocyanidins and anthoxanthins.

Flavans

The flavan class of polyphenols includes flavanols such as the catechins, which

are found in high concentration in tea leaves. Catechins and phenolic acids (e.g., tannins)

make up about 25% of the tea leaf, which also contains psychoactive compounds (e.g.,

caffeine; see psychoactive alkaloid section). Tea has been used medicinally for centuries,

likely because of these bioactive phytochemicals. Tea consumption is still very common

globally, but epidemiological evidence correlating tea consumption with the risk of

developing AD has been mixed. However, multiple lines of experimental evidence

suggest that tea may protect against oxidative stress (I. C. Burckhardt et al., 2008; Yan

Xu et al., 2010) and that some of tea's compounds may protect various AD-related

pathways. For example, a transgenic mouse study demonstrated that an extract of black

tea polyphenols significantly reduced memory impairment, oxidative damage, Aβ burden,

and apoptosis (Mathiyazahan, Justin Thenmozhi, & Manivasagam, 2015).

Isolated catechins found in tea have been studied more in depth. Epigallocatechin-

3-gallate (EGCG) is a well-characterized catechin found in tea that has been shown to decrease behavioral impairments, reduce Aβ production, and decrease y-secretase activity in transgenic mice (H. J. Lim et al., 2013). In another transgenic mouse study, EGCG treatment restored respiratory rates and membrane potential, reduced ROS production, and increased ATP levels by 50 to 85% in mitochondria isolated from the hippocampus, cortex, and striatum (Dragicevic et al., 2011). In addition to the neuroprotective effects of ECGC, a recent study of aging rats examined a tea extract rich in other catechins, but poor in ECGC. The data demonstrated improved learning and memory and reduced oxidative stress, suggesting that tea consumption is associated with multiple catechins having a synergistic neuroprotective effect above and beyond isolated tea catechins (Rodrigues et al., 2013). Overall, the phenolic acids and flavonoids found in tea offer multi-faceted neuroprotection from AD via multiple mechanisms.

Anthocyanidins

Anthocyanidins are water soluble pigments with potent with antioxidant and anti-inflammatory properties found in high concentrations in fruits such as the blueberry (Giacalone et al., 2015; Malin et al., 2011; Nica Sousa, Teixeira, & Soares, 2014). Rodent models of AD have shown that a blueberry enriched diet significantly reduced learning and memory impairments mediated by excitotoxicity and oxidative stress, decreased neuronal loss, and inhibited AChE activity (Duffy et al., 2008; Papandreou et al., 2009; Williams et al., 2008). In a recent study, a single drink containing blueberry flavonoids was given to 8-10-year-old children 2 hours before a brief memory assay and was associated with overall improved delayed recall, but increased susceptibility to proactive

interference (Whyte & Williams, 2015).

Anthoxanthins

Anthoxanthins are another class of flavonoid pigment that includes compounds such as the flavones and flavonols. Luteolin is a flavone found in the leaves and rinds of many plants, including celery, broccoli and citrus fruits that acts on multiple pathways associated with the development of AD. Reported effects in transgenic mice include decreases in both Aβ deposition and tau phosphorylation (which can ultimately lead to NFTs in humans). Other studies using rat models of AD suggest that luteolin protects against Aβ-induced cognitive impairment by regulating the cholinergic system, inhibiting oxidative stress, and prevented hippocampal cell death in a chemically-induced model of AD (H. Wang, Wang, Cheng, & Che, 2016; T.-X. Yu, Zhang, Guan, Wang, & Zhen, 2015). Additionally, luteolin has been shown to reduce neuroinflammation and Aβ deposition following experimental traumatic brain injury in transgenic mice (Sawmiller et al., 2014). Finally, luteolin demonstrates significant antioxidant action, regulates phosphorylation (R. Liu et al., 2009; Zhou, Chen, Xiong, Li, & Qu, 2012), inhibits mitochondrial dysfunction induced by myocardial insult, protects BBB permeability in AD rodent models, reduces apoptosis in Parkinson's disease rodent models, alleviates obesity-induced cognitive impairment in a rodent model of type-2 diabetes mellitus, and has anti-carcinogenic properties in an animal model of lung cancer (Guo, Li, Yu, & Chan, 2013; Y. Liu et al., 2014; Pratheeshkumar et al., 2014; D. Yu, Li, Tian, Liu, & Shang, 2015; J.-X. Zhang et al., 2017). Thus, like other polyphenols, luteolin seems to be readily available in the diet and may provide protection from age-related neuropathology from

several different angles.

Flavonols such as fisetin, quercetin, myricetin, and kaempferol have also demonstrated bioactive properties of interest to aging and AD research. For example, fisetin, which is found in strawberries and other fruits and vegetables, enhanced cognitive performance and reduced inflammation in a rodent model of induced neurodegeneration (Prakash, Gopinath, & Sudhandiran, 2013). Fisetin's affects appear to be in part attributable to increases in cAMP response element binding (CREB), which plays an important role in learning and memory mechanisms and has been shown to reduce Aβ plaque formation. Additionally, isolated preparations of quercetin and myricetin have been shown to reduce Aβ-related damage to muscarinic acetylcholine receptors (Hu, Ding, Zhou, & Xu, 2015; Ramezani, Darbandi, Khodagholi, & Hashemi, 2016).

Kaempferol and quercetin are flavonols found in especially high concentrations in the leaves of the gingko biloba tree, which have been used medicinally for centuries due to their purported cognitive enhancing properties. In addition to kaempferol and quercetin, ginkgo biloba also contains terpenes such as ginkgolides and bilobalides (see section on ginkgolides and bilobalides). It has most often been studied experimentally using an extract known as EGb761, which has been standardized to 24% polyphenol / 6% terpene content, allowing relatively easy comparisons between experimental studies. Multiple clinical trials have shown that daily treatment with EGb761 for a period of 12-24 weeks can provide mild cognitive improvements in elderly and demented patients (Herrschaft et al., 2012; Ihl, Tribanek, & Bachinskaya, 2012; Napryeyenko, Sonnik, & Tartakovsky, 2009). A study of several thousand non-demented elderly adults compared the effects of EGb761 to piracetam on cognitive functioning over a 20-year period.

Results indicated less cognitive decline in subjects taking EGb761 than those who reported regular use of piracetam (Amieva, Meillon, Helmer, Barberger-Gateau, & Dartigues, 2013). Another recent randomized, placebo-controlled trial of several hundred outpatients was conducted to demonstrate the efficacy and safety of EGb761 treatment for 24 weeks in patients with AD or vascular dementia. EGb76 treatment produced significant and clinically relevant improvements in cognition, psychopathology, functional measures, and quality of life for patients and caregivers. Importantly, no significant toxicities were observed (Herrschaft et al., 2012). However, in another randomized, placebo-controlled trial, adults aged 70 years or older who presented with initial memory complaints were administered EGb761 daily and followed for conversion to probable AD diagnoses. In these subjects, EGb761 did not reduce the risk of progression to AD compared with controls given a placebo (Schneider, 2012; Vellas et al., 2012). However, like many failed clinical trials of AD treatments, it is possible that the intervention was simply started too late, since neuropathology generally precedes the clinical symptoms by several years.

Several animal and in vitro studies have demonstrated that EGb761 can modulate multiple pathways related to both brain function and neuroprotection. For example, EGb761 has been shown to increase dopaminergic transmission in the rat PFC (Yoshitake, Yoshitake, & Kehr, 2010), increase production of brain derived neurotrophic factor in aged rats (Belviranlı & Okudan, 2014), improve mitochondrial respiration in vitro (Tendi et al., 2002), and attenuate lipid peroxidation and superoxide free radical production in a mouse model of Parkinson's disease (Rojas et al., 2008). In addition to its potent antioxidant properties, EGb761 also acts as an AChE inhibitor, so several studies

have compared its clinical effects to pharmaceutical AChE inhibitors. One study found that combined treatment with EGb761 and donepezil was superior to either compound alone and produced fewer side effects than mono-therapy with donepezil (Yancheva et al., 2009). Although AChE inhibitors have demonstrated mostly disappointing results in the treatment of AD, research into the efficacy of the extract persists because of its minimal side effect profile and other potential mechanisms of action (Weinmann, Roll, Schwarzbach, Vauth, & Willich, 2010). EGb761 has also been shown to reduce Aβ deposition, enhance CREB phosphorylation, and promote cell proliferation in the hippocampi of young and aged transgenic mice (Tchantchou, Xu, Wu, Christen, & Luo, 2007). In another study, transgenic mice that were given EGb761 for 20 weeks via dietary supplementation demonstrated significantly improved cognitive function, attenuated loss of synaptic proteins, inhibition of caspase-1, and less inflammation via microglia-induced secretion of TNF-α and IL-1β (X. Liu et al., 2015). This pattern of results suggests that the phytochemicals in EGb761 act on AD pathology via multiple synergistic mechanisms, including antioxidant, anti-inflammatory, and anti-AChE pathways (Eckert, 2012; Müller, Heiser, & Leuner, 2012).

Concerns about the bioavailability of phytochemicals like EGb761, such as their ability to cross the BBB, have led to recent investigations on the pharmacokinetics of these compounds. A rat study found that repeated oral administration of standard EGb761 doses for 1 week led to as much as a 10x increase in the plasma concentration of its flavonols components, which were also found in the hippocampus, frontal cortex, striatum, and cerebellum (Rangel-Ordóñez, Nöldner, Schubert-Zsilavecz, & Wurglics, 2010). Thus, although gingko biloba is generally not considered a dietary plant, the

available evidence suggests that readily available concentrated extracts may provide beneficial anti-aging and anti-AD effects via multiple pathways with a minimal side effect profile.

Terpenes

Terpenes are hydrocarbon compounds produced by plants (and some insects) that often have strong odors and an oily consistency. Terpenes of interest to aging and AD research include the ginkgolides and bilobalides (found in ginkgo biloba), huperzine A (found in Chinese club moss), and the phytocannabinoids (found in cannabis).

Ginkgolides and Bilobalides

As mentioned above, gingko biloba is often studied using EGb761, an extract that has been standardized to contain 24% polyphenols and 6% terpenes (the ginkgolides and bilobalides). Studies using EGb761 are discussed in more detail in the previous section, and it should be noted that its polyphenols and terpenes seem to act together in a synergistic fashion to provide its neuroprotective effects (Eckert, 2012; Müller et al., 2012). However, at least one study suggests that ginkgolide J, one of its terpenoid components, provided similar protection from the detrimental effects of Aβ on long term potentiation as the whole extract (Vitolo et al., 2009).

Huperzine A

Huperzine A is a terpene alkaloid with AChE inhibiting properties found in the toothed clubmoss plant. It has been shown to promote neurogenesis in the rodent dentate

gyrus (T. Ma et al., 2013) and protect mitochondria against Aβ deposition by preserving

membrane integrity and improving energy metabolism (Gao, Zheng, Yang, Tang, &

Zhang, 2009). Both huperzine A and Huprine X, which is synthesized by combining

components of huperzine A with a synthetic AChE inhibitor, improved learning and

memory in a transgenic mouse model of AD (X. Ma & Gang, 2008; Ratia et al., 2013).

However, recent clinical trials have yielded mixed results, and the low availability of

toothed clubmoss, along with the relatively poor performance of pharmaceutical

acetylcholinesterase inhibitors, has slowed progress (Rafii et al., 2011).

Cannabinoids

Cannabis is a plant with long history of both medicinal and recreational use.

Cannabis contains a wide variety of terpenes, collectively known as phytocannabinoids,

that bind with CB1 and CB2 cannabinoid receptors. CB1 receptors are expressed mainly

in the cerebral cortex and are thought to be responsible for cannabis' well-documented

psychoactive effects. CB2 receptors are expressed mainly in the periphery and are

thought to play a role in a variety of inflammatory processes. These compounds,

including tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), have

structural similarity to endogenous cannabinoid neurotransmitters such as anandamide

and 2-AG, and are antioxidant, anti-inflammatory, and neuroprotective against

excitotoxicity and acute brain damage (Haghani, Shabani, Javan, Motamedi, &

Janahmadi, 2012; Harvey, Ohlsson, Mååg, Musgrave, & Smid, 2012). Additionally,

phytocannabinoids have been demonstrated to enhance mitochondrial functioning (C.

Cao et al., 2014) and stimulate neurogenesis within the embryonic and adult

hippocampus (Jiang et al., 2005; Wolf et al., 2010).

Aging is associated with dysregulation of cannabinoid receptor expression (Bisogno & Di Marzo, 2010), and stimulation of cannabinoid receptors with synthetic cannabinoids has been shown to attenuate these effects (Marchalant et al., 2009; Marchalant, Cerbai, Brothers, & Wenk, 2008). A recent study demonstrated that THC restored cognitive performance in older mice, but, interestingly, the opposite effect was observed in younger mice (Bilkei-Gorzo et al., 2017). Several studies have suggested multiple mechanisms by which cannabinoids, including the phytocannabinoids found in cannabis, can also affect AD process. There is currently no conclusive epidemiological evidence on long-term cannabis users and a reduced incidence of AD, but multiple lines of experimental evidence suggest a possible protective effect. Although the relationship between cannabinoid receptors and AD pathogenesis remains unclear, cannabinoid receptor expression and the activity levels of enzymes that control endogenous cannabinoid concentrations change with the development of AD (Marchalant et al., 2009). Postmortem studies of AD and Down syndrome brains reveal consistently elevated levels of CB2 expression, whereas CB1 receptors are often reduced (J. H. Lee et al., 2010; Solas, Francis, Franco, & Ramirez, 2013) (Benito et al., 2003; Núñez et al., 2008; Tolón et al., 2009). These and other observations suggest that endogenous cannabinoids such as 2-AG mediate inflammatory and neuroprotective processes (X. Chen, Zhang, & Chen, 2011; Piro et al., 2012).

A study of transgenic mice that also lacked CB1 receptors reported that despite a decrease in Aβ plaque load, significant learning and memory deficits persisted, suggesting that CB1 receptor deficiency can worsen AD-related cognitive deficits

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independent of Aβ plaque load (Stumm et al., 2013). Another study showed that the rate of Aβ clearance across the BBB was doubled by stimulation of the endogenous cannabinoid 2-arachidonoylglycerol (2AG) via inhibition of endogenous cannabinoid-degrading enzymes (Bachmeier, Beaulieu-Abdelahad, Mullan, & Paris, 2013; Bisogno & Di Marzo, 2010). Furthermore, another study demonstrated that treatment with a synthetic CB2 agonist reduced Aβ-induced memory loss (Wu et al., 2013), and in vitro data shows that THC inhibits Aβ aggregation via indirect interaction with Aβ peptides (Eubanks et al., 2006). Finally, studies of synthetic cannabinoids have shown them to ameliorate cognitive impairment and neurodegeneration in multiple models of Aβ-induced neurotoxicity and neuroinflammation independent of antioxidant and/or psychoactive properties (R. Chen et al., 2012; Martín-Moreno et al., 2012; Martin-Moreno et al., 2011). Thus, cannabinoids, including those found in cannabis, seem to act on age-related and AD-specific neuropathological processes through multiple pathways, suggesting a potential role for exogenous (e.g., phyto- or synthetic) cannabinoids in the prevention and/or treatment of AD.

Organosulphurs

Garlic contains many aromatic sulfur-containing phytochemicals, including s-allyl cysteine (SAC) and di-allyl disulfide, collectively known as organosulfurs. Adding an aged garlic extract, SAC, or di-allyl-disulfide to the diets of transgenic mice has been shown to ameliorate cognitive deficits, reduce Aβ plaque formation, reduce abnormal tau build-up, and reduce oxidative damage (Asdaq, 2015; Chauhan, 2006; Colin-Gonzalez, Ali, Tunez, & Santamaria, 2015; Javed et al., 2011; Qu, Mossine, Cui, Sun, & Gu, 2016).

SAC has been shown to inhibit and reverse Aβ aggregation in vitro and in transgenic mice by binding directly to the Aβ peptide (Ray, Chauhan, & Lahiri, 2011). Another in vitro study examining the neuroprotective potential of SAC found reduced apoptosis that was not attributable to antioxidant activity, but rather to suppression of calpain proteins (Imai et al., 2014, 2016). The isolated components of SAC also appear to have AD-related neuroprotective properties, and may produce a synergistic effect in combination with di-allyl-disulfide. Together, these findings suggest that garlic and its organosulfur compounds may act on several pathways to reduce Aβ plaque formation and other AD neuropathology.

Fatty Acids

Omega-3 fatty acids, such as α-linolenic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are found mainly in flax, nuts, algae, and certain fish. DHA and EPA make up about 15% of the human brain's total fatty acids and 30-40% of its gray matter. Consuming omega-3 fatty acids can reduce inflammation, improve learning and memory, increase gray matter volume, and alter gut microbiota composition. DHA has been shown to protect against Aβ-induced neurotoxicity in transgenic mice and has demonstrated anti-inflammatory and anticancer properties (Calon et al., 2004; Lebbadi et al., 2011; Yuhai Zhao et al., 2011). In vitro studies have shown that DHA and EPA can reduce Aβ aggregation, increase production of neurotrophic substances, and decrease production of pro-inflammatory cytokines (Hjorth et al., 2013). Additionally, omega-3 derivatives can promote α-secretase processing of APP, which prevents the production of Aβ and leads instead to the production of the neuroprotective peptide sAPPα (Yuhai Zhao

et al., 2011). A recent study of AD patients found that 24 weeks of omega-3 supplementation produced increased levels of EPA and DHA in plasma and cerebrospinal fluid (CSF) that were inversely correlated with CSF levels of phosphorylated tau (Freund Levi et al., 2014). However, another recent study demonstrated that Aβ pathology may limit the ability of DHA to readily cross the BBB, which may explain why several clinical trials have yielded inconclusive or negative results, despite the high bioavailability of DHA (M. Burckhardt et al., 2016; Yassine et al., 2016).

Phytovitamins

Epidemiological evidence mentioned in Chapter 3 suggests a protective effect of dietary vitamins against the risk of developing AD, and experimental evidence with humans and rodents tends to support this idea. Tocopherols (isoforms of vitamin E) and folic acid (an isoform of vitamin B9) are found in several commonly consumed plants. A recent clinical trial of vitamin E supplementation in AD patients taking AChE inhibitors reported a 19% per year delay in clinical progression (Dysken et al., 2014), but recent clinical trials of vitamin E in isolation have yielded less promising results, suggesting that vitamin E may be better suited as a complementary therapy for AD (Farina et al., 2012). However, in a study of aged rats, vitamin E-supplementation improved age-related cognitive deficits (Takatsu, Owada, Abe, Nakano, & Urano, 2009), and several transgenic mouse studies have demonstrated beneficial AD-related effects of supplementing with vitamin E. For example, dietary administration of vitamin E to transgenic mice reduced Aβ deposition (Hashimoto et al., 2005) along with its associated oxidative stress and neuritic dystrophy (Zimmermann, Colciaghi, Cattabeni, & Di Luca,

2002), and it ameliorated behavioral impairments, oxidative stress, and injury-accelerated Aβ formation resulting from repetitive traumatic brain injury (Conte et al., 2004). Therefore, the data suggest that dietary tocopherols may protect the brain from Aβ deposition and its associated functional decline.

Other studies have focused on B vitamins, because dietary deficiencies have been associated with cognitive decline and an increase in AD-related neuropathology. For example, a study of elderly individuals with a vitamin B deficiency found that reversing the deficiency with folic acid (an isoform of vitamin B9 found in many fruits and vegetables) improved cognitive function after 14 weeks (Cheng et al., 2016). A transgenic mouse study looked at the effects of dietary folic acid deficiency on neuropathology in transgenic mice and reported significant neurodegeneration within the hippocampus, although Aβ levels were not affected (Kruman II et al., 2002). An in vitro study of folic acid deprivation demonstrated increased expression of the genes involved in encoding the γ- and β-secretases along with increased levels of Aβ (Fuso, Seminara, Cavallaro, D'Anselmi, & Scarpa, 2005). In a study of high dose B vitamin supplements given to healthy adult participants over 4-weeks, increased task-related functional brain activity (Barbey, 2016). However, a similar high dose combination of vitamins B6 and B12 was ineffective at slowing cognitive decline in individuals with mild to moderate AD, suggesting that vitamin B may be more effective as a preventive measure for AD than as an acute intervention for AD related cognitive decline (Aisen et al., 2008). Other trials of folic acid supplementation in humans have shown that its long-term consumption is associated with decreased plasma levels of Aβ and increased grey matter volume in the brain (Erickson et al., 2008; Flicker et al., 2008). These studies, along with data showing

the neuroprotective effects of folic acid on the developing nervous system and the anti-oxidant properties of dietary tocopherols, suggest that consuming phytovitamins may offer neuroprotection from oxidative stress that contributes to increased Aβ deposition and AD progression.

<p style="text-align:center">Psychoactive Alkaloids</p>

Caffeine

Although tea and coffee contain high levels of beneficial polyphenol compounds, the psychoactive alkaloid caffeine explains their global popularity. Caffeine functions as an insecticide in plants and as a psychostimulant in animals. Because its stimulant effects (resulting from its competitive inhibition of adenosine receptors in the brain) are not associated with the euphoria and addictive properties characterized by other psychostimulants (e.g., cocaine and amphetamines), caffeine has been used centuries throughout the globe as a general cognitive enhancer. Recent studies with animal models of AD have shown that caffeine consumption is associated with protection against oxidative stress, improved mitochondrial functioning and BBB permeability, increased expression of brain derived neurotrophic factor, and reduced Aβ deposition and associated cognitive deficits (C. Cao et al., 2009; Xuesong Chen et al., 2008; Dragicevic et al., 2012; Laurent et al., 2014; Prasanthi et al., 2010). One study compared pure caffeine to "crude" caffeine, which is derived from coffee during the decaffeination process and likely contains other compounds (e.g., phenolic acids). Both supplements had beneficial effects in a transgenic mouse model of AD, including neuroprotection from

Aβ-induced neuronal death via suppressed caspase-3 activity. However, crude caffeine was more effective in reducing learning and memory deficits, and only crude caffeine reduced hippocampal Aβ deposition, suggesting that "phyto"-caffeine may offer protection from AD-related processes above and beyond that produced by pure caffeine (Chu et al., 2012). Interestingly, "caffeinol" (a combination of caffeine and ethanol) has been shown to demonstrate potent synergistic neuroprotection in rodent models of stroke (Bednarski, Gasińska, Straszewski, Godek, & Tutka, 2015; Martin-Schild et al., 2009; X. Zhao et al., 2010). Caffeine's mild stimulant effects may improve cognition, and it appears to offer multiple synergistic pathways of neuroprotection from AD pathology, including inhibition of Aβ aggregation and protection from neurologic insult.

Nicotine

Nicotine is another alkaloid that protects the tobacco plant from insect predators and produces psychostimulant effects in animals, primarily due to its agonist action at nicotinic acetylcholine receptors. Like caffeine, nicotine has a long history of human use at least partially due to its stimulant and cognitive enhancement properties. Although some previous studies have demonstrated in both humans and animals that nicotine may have potential neuroprotective effects on AD pathology, further research has demonstrated that smokers are at a significantly higher risk of developing AD via multiple pathways (N. T. Aggarwal et al., 2006; Durazzo, Mattsson, & Weiner, 2014; Huang, Dong, Zhang, Wu, & Liu, 2009). Chronic nicotine administration in transgenic mouse models of AD has been shown to increase levels of brain-derived neurotrophic factor and prevent long-term memory impairment induced by Aβ deposition (Alkadhi,

Alzoubi, Srivareerat, & Tran, 2011; Srivareerat, Tran, Salim, Aleisa, & Alkadhi, 2011).

Possible mechanisms include activity at the nicotinic acetylcholine receptors, which

results in decreased oxidative damage, Aβ deposition, and apoptosis. In addition to the

potential cognitive enhancement, antioxidant, and anti-Aβ actions attributed to nicotine,

its psychoactive metabolite, nornicotine, has been shown to inhibit Aβ aggregation by

forming permanent covalent bonds with Aβ peptides (Kumar et al., 2011). These finding

suggest that pharmaceutical treatment with nicotine may provide positive benefits in the

treatment and/or prevention of AD.

CHAPTER FOUR

SUMMARY

The development of AD-related neuropathology and its associated behavioral deficits is related to the gradual accumulation of Aβ plaques and NFTs in the cortex over the lifespan. This causes increased oxidative stress and inflammation in the brain, leading to further Aβ deposition, neuronal degradation, and other downstream effects. A variety of acute or low-grade chronic neurological insults can accelerate this process, and current pharmacological treatment options appear to be only minimally beneficial.

In the absence of effective pharmaceutical therapies for AD, focusing on lifestyle factors associated with reducing risk of developing AD appears to be the most effective preventive measure. The difficulty of demonstrating consistent beneficial effects of phytochemicals in humans is not surprising, given the similar failures of pharmacological interventions. Nevertheless, several lines of research demonstrate that long-term consumption of various phytochemicals may attenuate multiple neuropathological processes associated with the development of AD. The results of experimental data from animal studies and clinical trials, along with a growing body of epidemiological studies, lend credibility to the idea that bioactive phytochemicals can have beneficial effects via multiple mechanisms related to general brain aging, including regulation of the intestinal/gut microbiome and BBB permeability, modulation of neurotransmitter degradation and binding, anti-inflammatory and antioxidant effects, reduced susceptibility to excitotoxicity and apoptosis, stimulation of neurogenesis and long-term potentiation, and maintenance of proper mitochondrial function and other cellular processes related to learning and memory (Akaishi et al., 2008; Maher, 2009).

Additionally, bioactive phytochemicals have demonstrated beneficial effects on multiple AD-specific processes, including inhibition of Aβ production by modulating enzymatic processes and reducing Aβ deposition in the brain by decreasing aggregation and increasing clearance.

Given that AD is progressive, insidious, and ultimately fatal disease effecting a significant portion of older individuals, delaying the onset of AD by even a slight margin would significantly impact its incidence. Mounting epidemiological and experimental evidence suggests that a lifetime of consuming an abundance of neuroprotective phytochemicals may provide significant protection from environmental and age-related insults that accelerate the progression of AD neuropathology (Bayram et al., 2012; Steele et al., 2007; Subash et al., 2015). Furthermore, diets containing a wide variety of bioactive phytochemicals from multiple plant sources may provide synergistic benefits over supplementing with isolated compounds (Berti et al., 2015; Uysal et al., 2013). Finally, chronic adherence to diets rich in diverse sources of bioactive dietary polyphenols may protect against neurodegenerative disorders such as AD, but may also confer additional health and age-related benefits.

REFERENCES

A. Armstrong, R. (2014). A critical analysis of the 'amyloid cascade hypothesis.' Folia Neuropathologica, 3(3), 211–225. https://doi.org/10.5114/fn.2014.45562

Abdul-Muneer, P. M., Chandra, N., & Haorah, J. (2015). Interactions of Oxidative Stress and Neurovascular Inflammation in the Pathogenesis of Traumatic Brain Injury. Molecular Neurobiology. https://doi.org/10.1007/s12035-014-8752-3

Adams, L. S., Seeram, N. P., Aggarwal, B. B., Takada, Y., Sand, D., & Heber, D. (2006). Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. Journal of Agricultural and Food Chemistry, 54(3), 980–985. https://doi.org/10.1021/jf052005r

Aggarwal, B. B., & Shishodia, S. (2004). Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: Reasoning for seasoning. Annals of the New York Academy of Sciences, 1030, 434–441. https://doi.org/10.1196/annals.1329.054

Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. Biochemical Pharmacology, 71(10), 1397–1421. https://doi.org/10.1016/j.bcp.2006.02.009

Aggarwal, N. T., Bienias, J. L., Bennett, D. A., Wilson, R. S., Morris, M. C., Schneider, J. A., … Evans, D. A. (2006). The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. Neuroepidemiology, 26(3), 140–146. https://doi.org/10.1159/000091654

Ahmed, M. A. E., El Morsy, E. M., & Ahmed, A. A. E. (2014). Pomegranate extract protects against cerebral ischemia/reperfusion injury and preserves brain DNA integrity in rats. Life Sciences, 110(2), 61–69. https://doi.org/10.1016/j.lfs.2014.06.023

Aisen, P. S., Schneider, L. S., Sano, M., Diaz-Arrastia, R., van Dyck, C. H., Weiner, M. F., … Alzheimer Disease Cooperative Study, for the. (2008). High-Dose B Vitamin Supplementation and Cognitive Decline in Alzheimer Disease: A Randomized Controlled Trial. JAMA, 300(15), 1774–1783. https://doi.org/10.1001/jama.300.15.1774

Akaishi, T., Morimoto, T., Shibao, M., Watanabe, S., Sakai-Kato, K., Utsunomiya-Tate, N., & Abe, K. (2008). Structural requirements for the flavonoid fisetin in inhibiting fibril formation of amyloid β protein. Neuroscience Letters, 444(3), 280–285. https://doi.org/10.1016/j.neulet.2008.08.052

Al-Kuraishy, H. M., & Al-Gareeb, A. I. (2016). Potential effects of pomegranate on lipid peroxidation and pro-inflammatory changes in daunorubicin-induced

cardiotoxicity in rats. International Journal of Preventive Medicine, 2016(June). https://doi.org/10.4103/2008-7802.184314

Alkadhi, K. A., Alzoubi, K. H., Srivareerat, M., & Tran, T. T. (2011). Chronic psychosocial stress exacerbates impairment of synaptic plasticity in β-amyloid rat model of Alzheimer's disease: prevention by nicotine. Current Alzheimer Research, 8(7), 718–731. https://doi.org/10.2174/156720511797633188

Alonso, R., Pisa, D., Marina, A. I., Morato, E., Rábano, A., & Carrasco, L. (2014). Fungal infection in patients with Alzheimer's disease. Journal of Alzheimer's Disease, 41(1), 301–311. https://doi.org/10.3233/JAD-132681

Alzheimer's Association. (2014). 2014 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia, 10(2), 1–80. https://doi.org/10.1016/j.jalz.2014.02.001

Ambigaipalan, P., De Camargo, A. C., & Shahidi, F. (2016). Phenolic Compounds of Pomegranate Byproducts (Outer Skin, Mesocarp, Divider Membrane) and Their Antioxidant Activities. Journal of Agricultural and Food Chemistry, 64(34), 6584–6604. https://doi.org/10.1021/acs.jafc.6b02950

Amieva, H., Meillon, C., Helmer, C., Barberger-Gateau, P., & Dartigues, J. F. (2013). Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up Population-Based Study. PLoS ONE, 8(1), e52755. https://doi.org/10.1371/journal.pone.0052755

Arntzen, K. A., Schirmer, H., Wilsgaard, T., & Mathiesen, E. B. (2010). Moderate wine consumption is associated with better cognitive test results: a 7-year follow up of 5033 subjects in the Tromsø Study. Acta Neurologica Scandinavica, 122(s190), 23–29. Retrieved from http://dx.doi.org/10.1111/j.1600-0404.2010.01371.x

Asdaq, S. M. B. (2015). Antioxidant and hypolipidemic potential of aged garlic extract and its constituent, s-allyl cysteine, in rats. Evidence-Based Complementary and Alternative Medicine, 2015, 328545. https://doi.org/10.1155/2015/328545

Atamna, H., Frey, W. H., & Ko, N. (2009). Human and rodent amyloid-Beta peptides differentially bind heme: Relevance to the human susceptibility to Alzheimer's disease. Archives of Biochemistry and Biophysics, 487(1), 59–65. https://doi.org/10.1016/j.abb.2009.05.003

Ates, O., Cayli, S., Altinoz, E., Gurses, I., Yucel, N., Sener, M., … Yologlu, S. (2007). Neuroprotection by resveratrol against traumatic brain injury in rats. Molecular and Cellular Biochemistry, 294(1–2), 137–144.

Aviram, M., Dornfeld, L., Rosenblat, M., Volkova, N., Kaplan, M., Hayek, T., … Fuhrman, B. (2000). Pomegranate juice consumption reduces oxidative stress and low density lipoprotein atherogenic modifications: studies in the atherosclerotic apolipoprotein E deficient mice and in humans. The American Journal of Clinical Nutrition, 151, 111. https://doi.org/10.1016/S0021-9150(00)80502-X

Aviram, Michael, Rosenblat, M., Gaitini, D., Nitecki, S., Hoffman, A., Dornfeld, L., … Hayek, T. (2004). Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. Clinical Nutrition, 23(3), 423–433. https://doi.org/10.1016/j.clnu.2003.10.002

Bachmeier, C., Beaulieu-Abdelahad, D., Mullan, M., & Paris, D. (2013). Role of the cannabinoid system in the transit of beta-amyloid across the blood-brain barrier. Molecular and Cellular Neuroscience, 56, 255–262. https://doi.org/10.1016/j.mcn.2013.06.004

Barage, S. H., & Sonawane, K. D. (2015). Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides, 52, 1–18. https://doi.org/10.1016/j.npep.2015.06.008

Barbey, A. K. (2016). Functional Brain Activity Changes after 4 Weeks Supplementation with a Multi-Vitamin / Mineral Combination : A Randomized , Double-Blind , Placebo-Controlled Trial Exploring Functional Magnetic Resonance Imaging and Steady-State Visual Evoked Potentials d. Frontiers in Aging Neuroscience, 8(December), 1–20. https://doi.org/10.3389/fnagi.2016.00288

Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J., de Jager, C. A., Erickson, K. I., … Squitti, R. (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. Neurobiology of Aging, 35(SUPPL.2), 1–5. https://doi.org/10.1016/j.neurobiolaging.2014.03.033

Bayer, T. A., & Wirths, O. (2010). Intracellular accumulation of amyloid-Beta - a predictor for synaptic dysfunction and neuron loss in Alzheimer's disease. Frontiers in Aging Neuroscience, 2(March), 8. https://doi.org/10.3389/fnagi.2010.00008

Bayram, B., Ozcelik, B., Grimm, S., Roeder, T., Schrader, C., Ernst, I. M. A., … Rimbach, G. (2012). A diet rich in olive oil phenolics reduces oxidative stress in the heart of SAMP8 mice by induction of Nrf2-dependent gene expression. Rejuvenation Research, 15(1), 71–81. https://doi.org/10.1089/rej.2011.1245

Bednarski, J., Gasińska, K., Straszewski, T., Godek, M., & Tutka, P. (2015). Caffeinol: a neuroprotective action in ischemic brain damage. Przeglad Lekarski, 72(11), 677–681. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27012130

Beer, C., Blacker, D., Hankey, G. J., & Puddey, I. B. (2011). Association of clinical and aetiologic subtype of acute ischaemic stroke with inflammation, oxidative stress and vascular function: A cross-sectional observational study. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research, 17(9), CR467-R473. https://doi.org/881931 [pii]

Belviranlı, M., & Okudan, N. (2014). The effects of Ginkgo biloba extract on cognitive functions in aged female rats: The role of oxidative stress and brain-derived neurotrophic factor. Behavioural Brain Research, 278C, 453–461. https://doi.org/10.1016/j.bbr.2014.10.032

Benito, C., Núñez, E., Tolón, R. M., Carrier, E. J., Rábano, A., Hillard, C. J., & Romero, J. (2003). Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. The Journal of Neuroscience, 23(35), 11136–11141. https://doi.org/23/35/11136 [pii]

BenSaad, L. A., Kim, K. H., Quah, C. C., Kim, W. R., & Shahimi, M. (2017). Anti-inflammatory potential of ellagic acid, gallic acid and punicalagin A&B isolated from Punica granatum. BMC Complementary and Alternative Medicine, 17(1), 47. https://doi.org/10.1186/s12906-017-1555-0

Bernardo, A., Harrison, F. E., McCord, M., Zhao, J., Bruchey, A., Davies, S. S., … McDonald, M. P. (2009). Elimination of GD3 synthase improves memory and reduces amyloid-β plaque load in transgenic mice. Neurobiology of Aging, 30(11), 1777–1791. https://doi.org/10.1016/j.neurobiolaging.2007.12.022

Berti, V., Murray, J., Davies, M., Spector, N., Tsui, W. H., Li, Y., … Mosconi, L. (2015). Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J Nutr Health Aging, 19(4), 413–423. https://doi.org/10.1007/s12603-014-0534-0

Bilkei-Gorzo, A., Albayram, O., Draffehn, A., Michel, K., Piyanova, A., Oppenheimer, H., … Zimmer, A. (2017). A chronic low dose of Δ9-tetrahydrocannabinol (THC) restores cognitive function in old mice. Nature Medicine, 23(6), 782–787. https://doi.org/10.1038/nm.4311

Bird, T. D. (2008). Genetic aspects of Alzheimer disease. Genetics in Medicine, 10(4), 231–239. https://doi.org/10.1097/GIM.0b013e31816b64dc

Biron, K. E., Dickstein, D. L., Gopaul, R., Jefferies, W. A., & Hendey, B. (2011). Amyloid Triggers Extensive Cerebral Angiogenesis Causing Blood Brain Barrier Permeability and Hypervascularity in Alzheimer's Disease. PLoS ONE, 6(8), e23789. https://doi.org/10.1371/journal.pone.0023789

Bishayee, A., Bhatia, D., Thoppil, R. J., Darvesh, A. S., Nevo, E., & Lansky, E. P. (2011). Pomegranate-mediated chemoprevention of experimental hepatocarcinogenesis involves Nrf2-regulated antioxidant mechanisms. Carcinogenesis, 32(6), 888–896. https://doi.org/10.1093/carcin/bgr045

Bishayee, A., Thoppil, R. J., Darvesh, A. S., Ohanyan, V., Meszaros, J. G., & Bhatia, D. (2013). Pomegranate phytoconstituents blunt the inflammatory cascade in a chemically induced rodent model of hepatocellular carcinogenesis. Journal of

Nutritional Biochemistry, 24(1), 178–187.
https://doi.org/10.1016/j.jnutbio.2012.04.009

Bisogno, T., & Di Marzo, V. (2010). Cannabinoid receptors and endocannabinoids: role in neuroinflammatory and neurodegenerative disorders. CNS & Neurological Disorders Drug Targets, 9(5), 564–573.

Block, M. L., & Hong, J. S. (2005). Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism. Progress in Neurobiology, 76(2), 77–98. https://doi.org/10.1016/j.pneurobio.2005.06.004

Bookheimer, S. Y., Renner, B. A., Ekstrom, A., Li, Z., Henning, S. M., Brown, J. A., … Small, G. W. (2013). Pomegranate juice augments memory and fMRI activity in middle-aged and older adults with mild memory complaints. Evidence-Based Complementary and Alternative Medicine, 2013. https://doi.org/10.1155/2013/946298

Borgesius, N. Z., de Waard, M. C., van der Pluijm, I., Omrani, A., Zondag, G. C. M., van der Horst, G. T. J., … Elgersma, Y. (2011). Accelerated age-related cognitive decline and neurodegeneration, caused by deficient DNA repair. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31(35), 12543–12553. https://doi.org/10.1523/JNEUROSCI.1589-11.2011

Braga, L. C., Shupp, J. W., Cummings, C., Jett, M., Takahashi, J. A., Carmo, L. S., … Nascimento, A. M. A. (2005). Pomegranate extract inhibits Staphylococcus aureus growth and subsequent enterotoxin production. Journal of Ethnopharmacology, 96(1–2), 335–339. https://doi.org/10.1016/j.jep.2004.08.034

Braskie, M. N., Jahanshad, N., Stein, J. L., Barysheva, M., McMahon, K. L., de Zubicaray, G. I., … Thompson, P. M. (2011). Common Alzheimer's Disease Risk Variant within the CLU Gene Affects White Matter Microstructure in Young Adults. Journal of Neuroscience, 31(18), 6764–6770. https://doi.org/10.1523/Jneurosci.5794-10.2011

Bredesen, D. E. (2009). Neurodegeneration in Alzheimer. Molecular Neurodegeneration, 10(1), 1–10. https://doi.org/10.1186/1750-1326-4-27

Brezová, V., Šlebodová, A., & Staško, A. (2009). Coffee as a source of antioxidants: An EPR study. Food Chemistry, 114(3), 859–868. https://doi.org/10.1016/j.foodchem.2008.10.025

Burckhardt, I. C., Gozal, D., Dayyat, E., Cheng, Y., Li, R. C., Goldbart, A. D., & Row, B. W. (2008). Green tea catechin polyphenols attenuate behavioral and oxidative responses to intermittent hypoxia. American Journal of Respiratory and Critical Care Medicine, 177(10), 1135–1141. https://doi.org/10.1164/rccm.200701-110OC

Burckhardt, M., Herke, M., Wustmann, T., Watzke, S., Langer, G., & Fink, A. (2016, April 11). Omega-3 fatty acids for the treatment of dementia. (M. Burckhardt,

Ed.), Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD009002.pub3

Burkholder-Cooley, N., Rajaram, S., Haddad, E., Fraser, G. E., & Jaceldo-Siegl, K. (2016). Comparison of polyphenol intakes according to distinct dietary patterns and food sources in the Adventist Health Study-2 cohort. British Journal of Nutrition, 1–8. https://doi.org/10.1017/S0007114516001331

Buttini, M., Masliah, E., Barbour, R., Grajeda, H., Motter, R., Johnson-Wood, K., … Games, D. (2005). β-Amyloid Immunotherapy Prevents Synaptic Degeneration in a Mouse Model of Alzheimer's Disease. The Journal of Neuroscience, 25(40), 9096 LP – 9101. https://doi.org/10.1523/JNEUROSCI.1697-05.2005

Cacace, R., Sleegers, K., & Van Broeckhoven, C. (2016). Molecular genetics of early-onset Alzheimer disease revisited. Alzheimer's and Dementia, 12(6), 733–748. https://doi.org/10.1016/j.jalz.2016.01.012

Calon, F., Lim, G. P., Yang, F., Morihara, T., Teter, B., Ubeda, O., … Cole, G. M. (2004). Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron, 43(5), 633–645. https://doi.org/10.1016/j.neuron.2004.08.013

Candore, G., Bulati, M., Caruso, C., Castiglia, L., Colonna-Romano, G., Di Bona, D., … Vasto, S. (2010). Inflammation, cytokines, immune response, apolipoprotein E, cholesterol, and oxidative stress in Alzheimer disease: therapeutic implications. Rejuvenation Res, 13(2–3), 301–313. https://doi.org/10.1089/rej.2009.0993

Cano-Lamadrid, M., Marhuenda-Egea, F. C., Hernandez, F., Rosas-Burgos, E. C., Burgos-Hernandez, A., & Carbonell-Barrachina, A. A. (2016). Biological Activity of Conventional and Organic Pomegranate Juices: Antioxidant and Antimutagenic Potential. Plant Foods for Human Nutrition, 71(4), 375–380. https://doi.org/10.1007/s11130-016-0569-y

Cao, C., Cirrito, J. R., Lin, X., Wang, L., Verges, D. K., Dickson, A., … Potter, H. (2009). Caffeine suppresses amyloid-β levels in plasma and brain of Alzheimer's disease transgenic mice. Journal of Alzheimer's Disease, 17(3), 681–697. https://doi.org/10.3233/JAD-2009-1071

Cao, C., Li, Y., Liu, H., Bai, G., Mayl, J., Lin, X., … Cai, J. (2014). The potential therapeutic effects of THC on Alzheimer's disease. Journal of Alzheimer's Disease : JAD, 42(3), 973–984. https://doi.org/10.3233/JAD-140093

Cao, K., Xu, J., Pu, W., Dong, Z., Sun, L., Zang, W., … Liu, J. (2015). Punicalagin, an active component in pomegranate, ameliorates cardiac mitochondrial impairment in obese rats via AMPK activation. Sci Rep, 5(July), 14014. https://doi.org/10.1038/srep14014

Capiralla, H., Vingtdeux, V., Zhao, H., Sankowski, R., Al-Abed, Y., Davies, P., & Marambaud, P. (2012). Resveratrol mitigates lipopolysaccharide- and Aβ-mediated microglial inflammation by inhibiting the TLR4/NF-κB/STAT signaling cascade. Journal of Neurochemistry, 120(3), 461–472. https://doi.org/10.1111/j.1471-4159.2011.07594.x

Castellano, J. M., Kim, J., Stewart, F. R., Jiang, H., DeMattos, R. B., Patterson, B. W., … Holtzman, D. M. (2011). Human apoE isoforms differentially regulate brain amyloid-β peptide clearance. Science Translational Medicine, 3(89), 89ra57. https://doi.org/10.1126/scitranslmed.3002156

Chamorro, Á., Dirnagl, U., Urra, X., & Planas, A. M. (2016). Neuroprotection in acute stroke: Targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. The Lancet Neurology.

Chauhan, N. B. (2006). Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. Journal of Ethnopharmacology, 108(3), 385–394. https://doi.org/10.1016/j.jep.2006.05.030

Chavez-Valdez, R., Martin, L. J., & Northington, F. J. (2012). Programmed necrosis: A prominent mechanism of cell death following neonatal brain injury. Neurology Research International, 2012. https://doi.org/10.1155/2012/257563

Chen, H., & Sang, S. (2014). Biotransformation of tea polyphenols by gut microbiota. Journal of Functional Foods, 7(1), 26–42. https://doi.org/10.1016/j.jff.2014.01.013

Chen, L. G., Liu, Y. C., Hsieh, C. W., Liao, B. C., & Wung, B. S. (2008). Tannin 1-alpha-O-galloylpunicalagin induces the calcium-dependent activation of endothelial nitric-oxide synthase via the phosphatidylinositol 3-kinase/Akt pathway in endothelial cells. Molecular Nutrition and Food Research, 52(10), 1162–1171. https://doi.org/10.1002/mnfr.200700335

Chen, R., Zhang, J., Wu, Y., Wang, D., Feng, G., Tang, Y.-P., … Chen, C. (2012). Monoacylglycerol Lipase Is a Therapeutic Target for Alzheimer's Disease. Cell Reports, 2(5), 1329–1339. https://doi.org/10.1016/j.celrep.2012.09.030

Chen, X., Zhang, J., & Chen, C. (2011). Endocannabinoid 2-arachidonoylglycerol protects neurons against β-amyloid insults. Neuroscience, 178, 159–168. https://doi.org/10.1016/j.neuroscience.2011.01.024

Chen, Xuesong, Gawryluk, J. W., Wagener, J. F., Ghribi, O., Geiger, J. D., Holash, J., … Stopa, E. (2008). Caffeine blocks disruption of blood brain barrier in a rabbit model of Alzheimer's disease. Journal of Neuroinflammation, 5(1), 12. https://doi.org/10.1186/1742-2094-5-12

Cheng, D., Kong, H., Pang, W., Yang, H., Lu, H., Huang, C., & Jiang, Y. (2016). B vitamin supplementation improves cognitive function in the middle aged and

elderly with hyperhomocysteinemia. Nutritional Neuroscience, 19(10), 461–466. https://doi.org/10.1179/1476830514Y.0000000136

Cherry, J. D., Olschowka, J. A., & O'Banion, M. (2014). Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. Journal of Neuroinflammation, 11(1), 98. https://doi.org/10.1186/1742-2094-11-98

Chiou, Y. S., Wu, J. C., Huang, Q., Shahidi, F., Wang, Y. J., Ho, C. T., & Pan, M. H. (2014). Metabolic and colonic microbiota transformation may enhance the bioactivities of dietary polyphenols. Journal of Functional Foods, 7(1), 3–25. https://doi.org/10.1016/j.jff.2013.08.006

Chu, Y.-F., Chang, W.-H., Black, R. M., Liu, J.-R., Sompol, P., Chen, Y., … Cheng, I. H. (2012). Crude caffeine reduces memory impairment and amyloid β1–42 levels in an Alzheimer's mouse model. Food Chemistry, 135(3), 2095–2102. https://doi.org/10.1016/j.foodchem.2012.04.148

Cohen, R. M., Rezai-Zadeh, K., Weitz, T. M., Rentsendorj, A., Gate, D., Spivak, I., … Town, T. (2013). A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric aβ, and frank neuronal loss. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 33(15), 6245–6256. https://doi.org/10.1523/JNEUROSCI.3672-12.2013

Colin-Gonzalez, A. L., Ali, S. F., Tunez, I., & Santamaria, A. (2015). On the antioxidant, neuroprotective and anti-inflammatory properties of S-allyl cysteine: An update. Neurochemistry International, 89, 83–91. https://doi.org/10.1016/j.neuint.2015.06.011

Conte, V., Uryu, K., Fujimoto, S., Yao, Y., Rokach, J., Longhi, L., … Praticò, D. (2004). Vitamin E reduces amyloidosis and improves cognitive function in Tg2576 mice following repetitive concussive brain injury. Journal of Neurochemistry, 90(3), 758–764. https://doi.org/10.1111/j.1471-4159.2004.02560.x

Court, J. A., Johnson, M., Religa, D., Keverne, J., Kalaria, R., Jaros, E., … Perry, E. K. (2005). Attenuation of Aβ deposition in the entorhinal cortex of normal elderly individuals associated with tobacco smoking. Neuropathology and Applied Neurobiology, 31(5), 522–535.

Covas, M. I., Gambert, P., Fitó, M., & de la Torre, R. (2010). Wine and oxidative stress: Up-to-date evidence of the effects of moderate wine consumption on oxidative damage in humans. Atherosclerosis. https://doi.org/10.1016/j.atherosclerosis.2009.06.031

Dai, Q., Borenstein, A. R., Wu, Y., Jackson, J. C., & Larson, E. B. (2006). Fruit and Vegetable Juices and Alzheimer's Disease: The Kame Project. The American Journal of Medicine, 119(9), 751–759. https://doi.org/10.1016/j.amjmed.2006.03.045

de Nigris, F., Williams-Ignarro, S., Lerman, L. O., Crimi, E., Botti, C., Mansueto, G., … Napoli, C. (2005). Beneficial effects of pomegranate juice on oxidation-sensitive genes and endothelial nitric oxide synthase activity at sites of perturbed shear stress. Proceedings of the National Academy of Sciences of the United States of America, 102(13), 4896–4901. https://doi.org/10.1073/pnas.0500998102

Demattos, R. B., Lu, J., Tang, Y., Racke, M. M., Delong, C. A., Tzaferis, J. A., … Hutton, M. L. (2012). A plaque-specific antibody clears existing beta-amyloid plaques in Alzheimer's disease mice. Neuron, 76(5), 908–920. https://doi.org/10.1016/j.neuron.2012.10.029

Devi, L., & Anandatheerthavarada, H. K. (2010). Mitochondrial trafficking of APP and alpha synuclein: Relevance to mitochondrial dysfunction in Alzheimer's and Parkinson's diseases. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1802(1), 11–19. https://doi.org/10.1016/j.bbadis.2009.07.007

Dong, J., Atwood, C. S., Anderson, V. E., Siedlak, S. L., Smith, M. A., Perry, G., & Carey, P. R. (2003). Metal binding and oxidation of amyloid-β within isolated senile plaque cores: Raman microscopic evidence. Biochemistry, 42(10), 2768–2773. https://doi.org/10.1021/bi0272151

Dragicevic, N., Delic, V., Cao, C., Copes, N., Lin, X., Mamcarz, M., … Bradshaw, P. C. (2012). Caffeine increases mitochondrial function and blocks melatonin signaling to mitochondria in Alzheimer's mice and cells. Neuropharmacology, 63(8), 1368–1379. https://doi.org/10.1016/j.neuropharm.2012.08.018

Dragicevic, N., Smith, A., Lin, X., Yuan, F., Copes, N., Delic, V., … Bradshaw, P. C. (2011). Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. Journal of Alzheimer's Disease, 26(3), 507–521. https://doi.org/10.3233/JAD-2011-101629

Duffy, K. B., Spangler, E. L., Devan, B. D., Guo, Z., Bowker, J. L., Janas, A. M., … Ingram, D. K. (2008). A blueberry-enriched diet provides cellular protection against oxidative stress and reduces a kainate-induced learning impairment in rats. Neurobiology of Aging, 29(11), 1680–1689. https://doi.org/10.1016/j.neurobiolaging.2007.04.002

Dulcich, M. S., & Hartman, R. E. (2013). Pomegranate supplementation improves affective and motor behavior in mice after radiation exposure. Evidence-Based Complementary and Alternative Medicine, 2013. https://doi.org/10.1155/2013/940830

Durazzo, T. C., Mattsson, N., & Weiner, M. W. (2014). Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. Alzheimer's & Dementia, 10(3), S122–S145. https://doi.org/10.1016/j.jalz.2014.04.009

Dysken, M. W., Sano, M., Asthana, S., Vertrees, J. E., Pallaki, M., Llorente, M., … Guarino, P. D. (2014). Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. Jama, 311(1), 33–44. https://doi.org/10.1001/jama.2013.282834

Eckert, A. (2012). Mitochondrial effects of Ginkgo biloba extract. International Psychogeriatrics, 24(S1), S18–S20. https://doi.org/10.1017/S1041610212000531

Elfalleh, W., Tlili, N., Nasri, N., Yahia, Y., Hannachi, H., Chaira, N., … Ferchichi, A. (2011). Antioxidant Capacities of Phenolic Compounds and Tocopherols from Tunisian Pomegranate (Punica granatum) Fruits. Journal of Food Science, 76(5), 707–713. https://doi.org/10.1111/j.1750-3841.2011.02179.x

Erickson, K. I., Suever, B. L., Prakash, R. S., Colcombe, S. J., McAuley, E., & Kramer, A. F. (2008). Greater intake of vitamins B6 and B12 spares gray matter in healthy elderly: A voxel-based morphometry study. Brain Research, 1199, 20–26. https://doi.org/10.1016/j.brainres.2008.01.030

Espín, J. C., Larrosa, M., García-Conesa, M. T., & Tomás-Barberán, F. (2013). Biological Significance of Urolithins, the Gut Microbial Ellagic Acid-Derived Metabolites: The Evidence So Far. Evidence-Based Complementary and Alternative Medicine, 2013, 270418. https://doi.org/10.1155/2013/270418

Esquivel, P., & Jiménez, V. M. (2012). Functional properties of coffee and coffee by-products. Food Research International, 46(2), 488–495. https://doi.org/10.1016/j.foodres.2011.05.028

Eubanks, L. M., Rogers, C. J., Beuscher, Koob, G. F., Olson, A. J., Dickerson, T. J., & Janda, K. D. (2006). A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology. Molecular Pharmaceutics, 3(6), 773–777. https://doi.org/10.1021/mp060066m

Farina, N., Isaac, M. G. E. K. N., Clark, A. R., Rusted, J., & Tabet, N. (2012). Vitamin E for Alzheimer's dementia and mild cognitive impairment. The Cochrane Database of Systematic Reviews, 11(11), CD002854. https://doi.org/10.1002/14651858.CD002854.pub3

Farr, S. A., Niehoff, M. L., Ceddia, M. A., Herrlinger, K. A., Lewis, B. J., Feng, S., … Morley, J. E. (2016). Effect of botanical extracts containing carnosic acid or rosmarinic acid on learning and memory in SAMP8 mice. Physiology & Behavior, 165, 328–338. https://doi.org/10.1016/j.physbeh.2016.08.013

Fawcett, J. R., Bordayo, E. Z., Jackson, K., Liu, H., Peterson, J., Svitak, A., & Frey II, W. H. (2002). Inactivation of the human brain muscarinic acetylcholine receptor by oxidative damage catalyzed by a low molecular weight endogenous inhibitor from Alzheimer's brain is prevented by pyrophosphate analogs, bioflavonoids and other antioxidants. Brain Research, 950(1), 10–20.

Fernández-García, J. C., Cardona, F., & Tinahones, F. J. (2013). Inflammation, oxidative stress and metabolic syndrome: dietary modulation. Current Vascular Pharmacology, 11(6), 906–919. https://doi.org/10.2174/15701611113116660175

Flicker, L., Martins, R. N., Thomas, J., Acres, J., Taddei, K., Vasikaran, S. D., … Almeida, O. P. (2008). B-vitamins reduce plasma levels of beta amyloid. Neurobiology of Aging (Vol. 29). https://doi.org/10.1016/j.neurobiolaging.2006.10.007

Frautschy, S. A., Hu, W., Kim, P., Miller, S. A., Chu, T., Harris-White, M. E., & Cole, G. M. (2001). Phenolic anti-inflammatory antioxidant reversal of Aβ-induced cognitive deficits and neuropathology. Neurobiology of Aging, 22(6), 993–1005. https://doi.org/10.1016/S0197-4580(01)00300-1

Freund Levi, Y., Vedin, I., Cederholm, T., Basun, H., Faxén Irving, G., Eriksdotter, M., … Palmblad, J. (2014). Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: The OmegAD study. Journal of Internal Medicine, 275(4), 428–436. https://doi.org/10.1111/joim.12166

Fuso, A., Seminara, L., Cavallaro, R. A., D'Anselmi, F., & Scarpa, S. (2005). S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. Molecular and Cellular Neuroscience, 28(1), 195–204. https://doi.org/10.1016/j.mcn.2004.09.007

Gao, X., Zheng, C. Y., Yang, L., Tang, X. C., & Zhang, H. Y. (2009). Huperzine A protects isolated rat brain mitochondria against β-amyloid peptide. Free Radical Biology and Medicine, 46(11), 1454–1462. https://doi.org/10.1016/j.freeradbiomed.2009.02.028

Gasperotti, M., Passamonti, S., Tramer, F., Masuero, D., Guella, G., Mattivi, F., & Vrhovsek, U. (2015). Fate of Microbial Metabolites of Dietary Polyphenols in Rats: Is the Brain Their Target Destination? ACS Chemical Neuroscience, 6(8), 1341–1352. https://doi.org/10.1021/acschemneuro.5b00051

Ghavipour, M., Sotoudeh, G., Tavakoli, E., Mowla, K., Hasanzadeh, J., & Mazloom, Z. (2016). Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. European Journal of Clinical Nutrition, (February), 1–5. https://doi.org/10.1038/ejcn.2016.151

Giacalone, M., Di Sacco, F., Traupe, I., Pagnucci, N., Forfori, F., & Giunta, F. (2015). Blueberry Polyphenols and Neuroprotection. In Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease (pp. 17–28). Elsevier. https://doi.org/10.1016/B978-0-12-411462-3.00002-3

Giannakopoulos, P., Herrmann, F. R., Bussière, T., Bouras, C., Kövari, E., Perl, D. P., … Hof, P. R. (2003). Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology, 60(9), 1495–1500. https://doi.org/10.1212/01.WNL.0000063311.58879.01

Gilman, S., Koller, M., Black, R. S., Jenkins, L., Griffith, S. G., Fox, N. C., … Orgogozo, J.-M. (2005). Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. Neurology, 64(9), 1553 LP – 1562. https://doi.org/10.1212/01.WNL.0000159740.16984.3C

Gray, S. L., Anderson, M. L., Crane, P. K., Breitner, J. C. S., McCormick, W., Bowen, J. D., … Larson, E. (2008). Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. Journal of the American Geriatrics Society, 56(2), 291–295.

Guo, D.-J., Li, F., Yu, P. H.-F., & Chan, S.-W. (2013). Neuroprotective effects of luteolin against apoptosis induced by 6-hydroxydopamine on rat pheochromocytoma PC12 cells. Pharmaceutical Biology, 51(2), 190–196. https://doi.org/10.3109/13880209.2012.716852

Haghani, M., Shabani, M., Javan, M., Motamedi, F., & Janahmadi, M. (2012). CB1 cannabinoid receptor activation rescues amyloid β-induced alterations in behaviour and intrinsic electrophysiological properties of rat hippocampal CA1 pyramidal neurones. Cellular Physiology and Biochemistry : International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology, 29(3–4), 391–406. https://doi.org/10.1159/000338494

Hartman, R E. (2009). Actions of Bioactive Phytochemicals in Cell Function and Alzheimer's Disease Pathology. Micronutrients and Brain Health, 1–18.

Hartman, Richard E., Lee, J. M., Zipfel, G. J., & Wozniak, D. F. (2005). Characterizing learning deficits and hippocampal neuron loss following transient global cerebral ischemia in rats. Brain Research, 1043(1–2), 48–56. https://doi.org/10.1016/j.brainres.2005.02.030

Hartman, Richard E, Izumi, Y., Bales, K. R., Paul, S. M., Wozniak, D. F., & Holtzman, D. M. (2005). Treatment with an Amyloid-β Antibody Ameliorates Plaque Load, Learning Deficits, and Hippocampal Long-Term Potentiation in a Mouse Model of Alzheimer's Disease. The Journal of Neuroscience, 25(26), 6213 LP – 6220. https://doi.org/10.1523/JNEUROSCI.0664-05.2005

Hartman, Richard E, Shah, A., Fagan, A. M., Schwetye, K. E., Parsadanian, M., Schulman, R. N., … Holtzman, D. M. (2006). Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiology of Disease, 24(3), 506–515. https://doi.org/10.1016/j.nbd.2006.08.006

Harvey, B. S., Ohlsson, K. S., Mååg, J. L. V., Musgrave, I. F., & Smid, S. D. (2012). Contrasting protective effects of cannabinoids against oxidative stress and amyloid-β evoked neurotoxicity in vitro. NeuroToxicology, 33(1), 138–146. https://doi.org/10.1016/j.neuro.2011.12.015

Hashimoto, M., Tanabe, Y., Fujii, Y., Kikuta, T., Shibata, H., & Shido, O. (2005). Chronic Administration of Docosahexaenoic Acid Ameliorates the Impairment of Spatial Cognition Learning Ability in Amyloid β–Infused Rats. The Journal of Nutrition, 135(3), 549–555. https://doi.org/10.1093/jn/135.3.549

Head, E., Azizeh, B. Y., Lott, I. T., Tenner, a J., Cotman, C. W., & Cribbs, D. H. (2001). Complement association with neurons and beta-amyloid deposition in the brains of aged individuals with Down Syndrome. Neurobiology of Disease, 8(2), 252–265. https://doi.org/10.1006/nbdi.2000.0380

Heber, D. (2011). Pomegranate Ellagitannins. Herbal Medicine: Biomolecular and Clinical Aspects, 1–9. https://doi.org/doi:10.1201/b10787-11

Hedskog, L., Pinho, C. M., Filadi, R., Rönnbäck, A., Hertwig, L., Wiehager, B., … Ankarcrona, M. (2013). Modulation of the endoplasmic reticulum-mitochondria interface in Alzheimer's disease and related models. Proceedings of the National Academy of Sciences of the United States of America, 110(19), 7916–7921. https://doi.org/10.1073/pnas.1300677110

Herrschaft, H., Nacu, A., Likhachev, S., Sholomov, I., Hoerr, R., & Schlaefke, S. (2012). Ginkgo biloba extract EGb 761 ® in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. Journal of Psychiatric Research, 46(6), 716–723. https://doi.org/10.1016/j.jpsychires.2012.03.003

Hjorth, E., Zhu, M., Toro, V. C., Vedin, I., Palmblad, J., Cederholm, T., … Schultzberg, M. (2013). Omega-3 fatty acids enhance phagocytosis of alzheimer's disease-related amyloid-β42 by human microglia and decrease inflammatory markers. Journal of Alzheimer's Disease, 35(4), 697–713.

Hochgräfe, K., Sydow, A., & Mandelkow, E. M. (2013). Regulatable transgenic mouse models of Alzheimer disease: Onset, reversibility and spreading of Tau pathology. FEBS Journal. https://doi.org/10.1111/febs.12250

Houlden, A., Goldrick, M., Brough, D., Vizi, E. S., Lenart, N., Martinecz, B., … Denes, A. (2016). Brain injury induces specific changes in the caecal microbiota of mice via altered autonomic activity and mucoprotein production. Brain, Behavior, and Immunity, 57, 10–20. https://doi.org/10.1016/j.bbi.2016.04.003

Howell, A. B., & Souza, D. H. D. (2013). The pomegranate: effects on bacteria and viruses that influence human health effects on human bacteria bacteria that affect

the human body. Evidence-Based Complementary and Alternative Medicine, 2013.

Hu, X.-T., Ding, C., Zhou, N., & Xu, C. (2015). Quercetin protects gastric epithelial cell from oxidative damage in vitro and in vivo. European Journal of Pharmacology, 754, 115–124. https://doi.org/10.1016/j.ejphar.2015.02.007

Huang, C.-Q., Dong, B.-R., Zhang, Y.-L., Wu, H.-M., & Liu, Q.-X. (2009). Association of Cognitive Impairment With Smoking, Alcohol Consumption, Tea Consumption, and Exercise Among Chinese Nonagenarians/Centenarians. Cognitive and Behavioral Neurology, 22(3), 190–196. https://doi.org/10.1097/WNN.0b013e3181b2790b

Hughes, T. F., Andel, R., Small, B. J., Borenstein, A. R., Mortimer, J. A., Wolk, A., … Gatz, M. (2010). Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins. The American Journal of Geriatric Psychiatry, 18(5), 413–420. https://doi.org/10.1097/JGP.0b013e3181c65250

Husari, A., Hashem, Y., Bitar, H., Dbaibo, G., Zaatari, G., & El Sabban, M. (2016). Antioxidant activity of pomegranate juice reduces emphysematous changes and injury secondary to cigarette smoke in an animal model and human alveolar cells. International Journal of COPD, 11, 227–237. https://doi.org/10.2147/COPD.S97027

Ihl, R., Tribanek, M., & Bachinskaya, N. (2012). Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761 ® in Alzheimer's Disease and vascular dementia: Results from a randomised controlled trial. Pharmacopsychiatry, 45(2), 41–46. https://doi.org/10.1055/s-0031-1291217

Imai, T., Kosuge, Y., Endo-Umeda, K., Miyagishi, H., Ishige, K., Makishima, M., & Ito, Y. (2014). Protective effect of S-allyl-l-cysteine against endoplasmic reticulum stress-induced neuronal death is mediated by inhibition of calpain. In Amino Acids (Vol. 46, pp. 385–393). https://doi.org/10.1007/s00726-013-1628-4

Imai, T., Kosuge, Y., Saito, H., Uchiyama, T., Wada, T., Shimba, S., … Ito, Y. (2016). Neuroprotective effect of S-allyl-l-cysteine derivatives against endoplasmic reticulum stress-induced cytotoxicity is independent of calpain inhibition. Journal of Pharmacological Sciences, 130(3), 185–188. https://doi.org/10.1016/j.jphs.2016.03.004

Imtiaz, B., Tolppanen, A.-M., Kivipelto, M., & Soininen, H. (2014). Future directions in Alzheimer's disease from risk factors to prevention. Biochemical Pharmacology, 88(4), 661–670. https://doi.org/10.1016/j.bcp.2014.01.003

Iturriaga, R., Moya, E. a, & Del Rio, R. (2015). Inflammation and oxidative stress during intermittent hypoxia: the impact on chemoreception. Experimental Physiology, 100(2), 149–155. https://doi.org/10.1113/expphysiol.2014.079525

Javed, H., Khan, M. M., Khan, A., Vaibhav, K., Ahmad, A., Khuwaja, G., … Islam, F. (2011). S-allyl cysteine attenuates oxidative stress associated cognitive impairment and neurodegeneration in mouse model of streptozotocin-induced experimental dementia of Alzheimer's type. Brain Research, 1389, 133–142. https://doi.org/10.1016/j.brainres.2011.02.072

Jelic, S., & Le Jemtel, T. H. (2008). Inflammation, Oxidative Stress, and the Vascular Endothelium in Obstructive Sleep Apnea. Trends in Cardiovascular Medicine. https://doi.org/10.1016/j.tcm.2008.11.008

Jiang, W., Zhang, Y., Xiao, L., Van Cleemput, J., Ji, S. P., Bai, G., & Zhang, X. (2005). Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. Journal of Clinical Investigation, 115(11), 3104–3116. https://doi.org/10.1172/JCI25509

Jofre-Monseny, L., Minihane, A.-M., & Rimbach, G. (2008). Impact of apoE genotype on oxidative stress, inflammation and disease risk. Molecular Nutrition & Food Research, 52(1), 131–145. https://doi.org/10.1002/mnfr.200700322

Johanningsmeier, S. D., & Harris, G. K. (2011). Pomegranate as a Functional Food and Nutraceutical Source. Annual Review of Food Science and Technology, 2(1), 181–201. https://doi.org/10.1146/annurev-food-030810-153709

Joseph, J., Cole, G., Head, E., & Ingram, D. (2009). Nutrition, brain aging, and neurodegeneration. Journal of Neuroscience, 29(41), 12795–12801. https://doi.org/10.1523/JNEUROSCI.3520-09.2009

Kang, S. S., Jeraldo, P. R., Kurti, A., Miller, M. E., Cook, M. D., Whitlock, K., … Wishart, D. (2014). Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Molecular Neurodegeneration, 9(1), 36. https://doi.org/10.1186/1750-1326-9-36

Kaplan, M., Hayek, T., Raz, a, Coleman, R., Dornfeld, L., Vaya, J., & Aviram, M. (2001). Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid peroxidation, cellular cholesterol accumulation and development of atherosclerosis. The Journal of Nutrition, 131(8), 2082–2089. https://doi.org/PMID: 11481398

Karuppagounder, S. S., Pinto, J. T., Xu, H., Chen, H. L., Beal, M. F., & Gibson, G. E. (2009). Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. Neurochemistry International, 54(2), 111–118. https://doi.org/10.1016/j.neuint.2008.10.008

Kiko, T., Nakagawa, K., Satoh, A., Tsuduki, T., Furukawa, K., Arai, H., & Miyazawa, T. (2012). Amyloid β Levels in Human Red Blood Cells. PLoS ONE, 7(11), 1–6. https://doi.org/10.1371/journal.pone.0049620

Kimura, R., MacTavish, D., Yang, J., Westaway, D., & Jhamandas, J. H. (2012). Beta amyloid-induced depression of hippocampal long-term potentiation is mediated through the amylin receptor. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 32(48), 17401–17406. https://doi.org/10.1523/JNEUROSCI.3028-12.2012

Kitazawa, M., Medeiros, R., & M. LaFerla, F. (2012). Transgenic Mouse Models of Alzheimer Disease: Developing a Better Model as a Tool for Therapeutic Interventions. Current Pharmaceutical Design, 18(8), 1131–1147. https://doi.org/10.2174/138161212799315786

Köbe, T., Witte, A. V., Schnelle, A., Tesky, V. A., Pantel, J., Schuchardt, J.-P., … Flöel, A. (2017). Impact of Resveratrol on Glucose Control, Hippocampal Structure and Connectivity, and Memory Performance in Patients with Mild Cognitive Impairment. Frontiers in Neuroscience, 11. https://doi.org/10.3389/fnins.2017.00105

Kotilinek, L. A., Westerman, M. A., Wang, Q., Panizzon, K., Lim, G. P., Simonyi, A., … Ashe, K. H. (2008). Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. Brain : A Journal of Neurology, 131(Pt 3), 651–664. https://doi.org/10.1093/brain/awn008

Krüger, J., Moilanen, V., Majamaa, K., & Remes, A. M. (2012). Molecular Genetic Analysis of the APP, PSEN1, and PSEN2 Genes in Finnish Patients With Early-onset Alzheimer Disease and Frontotemporal Lobar Degeneration. Alzheimer Disease & Associated Disorders, 26(3), 272–276. https://doi.org/10.1097/WAD.0b013e318231e6c7

Kruman II, Kumaravel, T. S., Lohani, A., Pedersen, W. A., Cutler, R. G., Kruman, Y., … Mattson, M. P. (2002). Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci, 22(5), 1752–1762. https://doi.org/22/5/1752 [pii]

Kumar, P., Pillay, V., Choonara, Y. E., Modi, G., Naidoo, D., & Du Toit, L. C. (2011). In Silico Theoretical Molecular Modeling for Alzheimer's Disease: The Nicotine-Curcumin Paradigm in Neuroprotection and Neurotherapy. International Journal of Molecular Sciences, 12(12), 694–724. https://doi.org/10.3390/ijms12010694

Kumaraswamy, P., Sethuraman, S., & Krishnan, U. M. (2013). Mechanistic Insights of Curcumin Interactions with the Core-Recognition Motif of β-Amyloid Peptide. Journal of Agricultural and Food Chemistry, 61(13), 3278–3285. https://doi.org/10.1021/jf4000709

Kwak, H.-M., Jeon, S.-Y., Sohng, B.-H., Kim, J.-G., Lee, J.-M., Lee, K.-B., … Song, K.-S. (2005). β-Secretase(BACE1) inhibitors from pomegranate (Punica granatum)

husk. Archives of Pharmacal Research, 28(12), 1328–1332. https://doi.org/10.1007/BF02977896

Laird, M. D., Sukumari-Ramesh, S., Swift, A. E. B., Meiler, S. E., Vender, J. R., & Dhandapani, K. M. (2010). Curcumin attenuates cerebral edema following traumatic brain injury in mice: A possible role for aquaporin-4? Journal of Neurochemistry, 113(3), 637–648.

Larrosa, M., González-Sarrías, A., Yáñez-Gascón, M. J., Selma, M. V., Azorín-Ortuño, M., Toti, S., … Espín, J. C. (2010). Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. Journal of Nutritional Biochemistry, 21(8), 717–725. https://doi.org/10.1016/j.jnutbio.2009.04.012

Lau, F. C., Shukitt-Hale, B., & Joseph, J. A. (2005). The beneficial effects of fruit polyphenols on brain aging. Neurobiology of Aging, 26(SUPPL.), 128–132. https://doi.org/10.1016/j.neurobiolaging.2005.08.007

Laurent, C., Eddarkaoui, S., Derisbourg, M., Leboucher, A., Demeyer, D., Carrier, S., … Blum, D. (2014). Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology. Neurobiology of Aging, 35(9), 2079–2090. https://doi.org/10.1016/j.neurobiolaging.2014.03.027

Lebbadi, M., Julien, C., Phivilay, A., Tremblay, C., Emond, V., Kang, J. X., & Calon, F. (2011). Endogenous conversion of omega-6 into omega-3 fatty acids improves neuropathology in an animal model of Alzheimer's disease. Journal of Alzheimer's Disease, 27(4), 853–869. https://doi.org/10.3233/JAD-2011-111010

Lee, E. B., Leng, L. Z., Zhang, B., Kwong, L., Trojanowski, J. Q., Abel, T., & Lee, V. M.-Y. (2006). Targeting amyloid-beta peptide (Abeta) oligomers by passive immunization with a conformation-selective monoclonal antibody improves learning and memory in Abeta precursor protein (APP) transgenic mice. The Journal of Biological Chemistry, 281(7), 4292–4299. https://doi.org/10.1074/jbc.M511018200

Lee, J. H., Agacinski, G., Williams, J. H., Wilcock, G. K., Esiri, M. M., Francis, P. T., … Lai, M. K. P. (2010). Intact cannabinoid CB1 receptors in the Alzheimer's disease cortex. Neurochemistry International, 57(8), 985–989. https://doi.org/10.1016/j.neuint.2010.10.010

Lefèvre-Arbogast, S., Féart, C., Dartigues, J.-F., Helmer, C., Letenneur, L., & Samieri, C. (2016). Dietary B Vitamins and a 10-Year Risk of Dementia in Older Persons. Nutrients, 8(12), 761. https://doi.org/10.3390/nu8120761

Legua, P., Melgarejo, P., Abdelmajid, H., Martínez, J. J., Martínez, R., Ilham, H., … Hernández, F. (2012). Total phenols and antioxidant capacity in 10 moroccan

pomegranate varieties. Journal of Food Science, 77(1), 115–120.
https://doi.org/10.1111/j.1750-3841.2011.02516.x

Lemere, C. A., Maier, M., Jiang, L., Peng, Y., & Seabrook, T. J. (2006). Amyloid-Beta
Immunotherapy for the Prevention and Treatment of Alzheimer Disease: Lessons
from Mice, Monkeys, and Humans. Rejuvenation Research, 9(1), 77–84.
https://doi.org/10.1089/rej.2006.9.77

Lim, G. P., Chu, T., Yang, F., Beech, W., Frautschy, S. a, & Cole, G. M. (2001). The
curry spice curcumin reduces oxidative damage and amyloid pathology in an
Alzheimer transgenic mouse. The Journal of Neuroscience: The Official Journal
of the Society for Neuroscience, 21(21), 8370–8377.

Lim, H. J., Shim, S. B., Jee, S. W., Lee, S. H., Lim, C. J., Hong, J. T., … Hwang, D. Y.
(2013). Green tea catechin leads to global improvement among Alzheimer's
disease-related phenotypes in NSE/hAPP-C105 Tg mice. The Journal of
Nutritional Biochemistry, 24(7), 1302–1313.
https://doi.org/10.1016/j.jnutbio.2012.10.005

Liu, R., Gao, M., Qiang, G.-F., Zhang, T.-T., Lan, X., Ying, J., & Du, G.-H. (2009). The
anti-amnesic effects of luteolin against amyloid β25–35 peptide-induced toxicity
in mice involve the protection of neurovascular unit. Neuroscience, 162(4), 1232–
1243. https://doi.org/10.1016/j.neuroscience.2009.05.009

Liu, X., Hao, W., Qin, Y., Decker, Y., Wang, X., Burkart, M., … Liu, Y. (2015). Long-
term treatment with Ginkgo biloba extract EGb 761 improves symptoms and
pathology in a transgenic mouse model of Alzheimer's disease. Brain, Behavior,
and Immunity, 46, 121–131. https://doi.org/10.1016/j.bbi.2015.01.011

Liu, Y., Fu, X., Lan, N., Li, S., Zhang, J., Wang, S., … Zhang, L. (2014). Luteolin
protects against high fat diet-induced cognitive deficits in obesity mice.
Behavioural Brain Research, 267, 178–188.
https://doi.org/10.1016/j.bbr.2014.02.040

Loren, D. J., Seeram, N. P., Schulman, R. N., & Holtzman, D. M. (2005). Maternal
dietary supplementation with pomegranate juice is neuroprotective in an animal
model of neonatal hypoxic-ischemic brain injury. Pediatric Research, 57(6), 858–
864. https://doi.org/10.1203/01.PDR.0000157722.07810.15

Lucarini, R., Bernardes, W. A., Ferreira, D. S., Tozatti, M. G., Furtado, R., Bastos, J. K.,
… Cunha, W. R. (2013). In vivo analgesic and anti-inflammatory activities of
Rosmarinus officinalis aqueous extracts, rosmarinic acid and its acetyl ester
derivative. Pharmaceutical Biology, 51(9), 1087–1090.
https://doi.org/10.3109/13880209.2013.776613

Ludwig, I. A., Sanchez, L., Caemmerer, B., Kroh, L. W., De Peña, M. P., & Cid, C.
(2012). Extraction of coffee antioxidants: Impact of brewing time and method.

Food Research International, 48(1), 57–64.
https://doi.org/10.1016/j.foodres.2012.02.023

Ma, T., Gong, K., Yan, Y., Zhang, L., Tang, P., Zhang, X., & Gong, Y. (2013).
Huperzine A promotes hippocampal neurogenesis in vitro and in vivo. Brain
Research, 1506, 35–43. https://doi.org/10.1016/j.brainres.2013.02.026

Ma, X., & Gang, D. R. (2008). In vitro production of huperzine A, a promising drug
candidate for Alzheimer's disease. Phytochemistry, 69(10), 2022–2028.
https://doi.org/10.1016/j.phytochem.2008.04.017

Maher, P. (2009). Modulation of multiple pathways involved in the maintenance of
neuronal function during aging by fisetin. Genes & Nutrition, 4(4), 297–307.
https://doi.org/10.1007/s12263-009-0142-5

Malin, D. H., Lee, D. R., Goyarzu, P., Chang, Y.-H., Ennis, L. J., Beckett, E., … Joseph,
J. A. (2011). Basic nutritional investigation Short-term blueberry-enriched diet
prevents and reverses object recognition memory loss in aging rats. Nutrition, 27,
338–342. https://doi.org/10.1016/j.nut.2010.05.001

Mangialasche, F., Solomon, A., Winblad, B., Mecocci, P., & Kivipelto, M. (2010).
Alzheimer's disease: clinical trials and drug development. The Lancet Neurology,
9(7), 702–716. https://doi.org/https://doi.org/10.1016/S1474-4422(10)70119-8

Marchalant, Y., Brothers, H. M., Norman, G. J., Karelina, K., DeVries, A. C., & Wenk,
G. L. (2009). Cannabinoids attenuate the effects of aging upon neuroinflammation
and neurogenesis. Neurobiology of Disease, 34(2), 300–307.
https://doi.org/10.1016/j.nbd.2009.01.014

Marchalant, Y., Cerbai, F., Brothers, H. M., & Wenk, G. L. (2008). Cannabinoid receptor
stimulation is anti-inflammatory and improves memory in old rats. Neurobiology
of Aging, 29(12), 1894–1901.
https://doi.org/10.1016/j.neurobiolaging.2007.04.028

Marín, L., Miguélez, E. M., Villar, C. J., & Lombó, F. (2015). Bioavailability of dietary
polyphenols and gut microbiota metabolism: Antimicrobial properties. BioMed
Research International, 2015. https://doi.org/10.1155/2015/905215

Mark, P. (2010). The impact of dietary energy intake on cognitive aging, 2(March), 1–12.
https://doi.org/10.3389/neuro.24.005.2010

Martín-Moreno, A. M., Brera, B., Spuch, C., Carro, E., García-García, L., Delgado, M.,
… de Ceballos, M. L. (2012). Prolonged oral cannabinoid administration prevents
neuroinflammation, lowers β-amyloid levels and improves cognitive performance
in Tg APP 2576 mice. Journal of Neuroinflammation, 9(1), 511.
https://doi.org/10.1186/1742-2094-9-8

Martin-Moreno, A. M., Reigada, D., Ramirez, B. G., Mechoulam, R., Innamorato, N., Cuadrado, A., & de Ceballos, M. L. (2011). Cannabidiol and Other Cannabinoids Reduce Microglial Activation In Vitro and In Vivo: Relevance to Alzheimer's Disease. Molecular Pharmacology, 79(6), 964–973. https://doi.org/10.1124/mol.111.071290

Martin-Schild, S., Hallevi, H., Shaltoni, H., Barreto, A. D., Gonzales, N. R., Aronowski, J., … Grotta, J. C. (2009). Combined Neuroprotective Modalities Coupled with Thrombolysis in Acute Ischemic Stroke: A Pilot Study of Caffeinol and Mild Hypothermia. Journal of Stroke and Cerebrovascular Diseases, 18(2), 86–96. https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.09.015

Masci, A., Coccia, A., Lendaro, E., Mosca, L., Paolicelli, P., & Cesa, S. (2016). Evaluation of different extraction methods from pomegranate whole fruit or peels and the antioxidant and antiproliferative activity of the polyphenolic fraction. Food Chemistry, 202, 59–69. https://doi.org/10.1016/j.foodchem.2016.01.106

Mathiyazahan, D. B., Justin Thenmozhi, A., & Manivasagam, T. (2015). Protective effect of black tea extract against aluminium chloride-induced Alzheimer's disease in rats: A behavioural, biochemical and molecular approach. Journal of Functional Foods, 16, 423–435. https://doi.org/10.1016/j.jff.2015.05.001

Matos, M., Augusto, E., Oliveira, C. R., & Agostinho, P. (2008). Amyloid-beta peptide decreases glutamate uptake in cultured astrocytes: Involvement of oxidative stress and mitogen-activated protein kinase cascades. Neuroscience, 156(4), 898–910. https://doi.org/10.1016/j.neuroscience.2008.08.022

Matthaiou, C. M., Goutzourelas, N., Stagos, D., Sarafoglou, E., Jamurtas, A., Koulocheri, S. D., … Kouretas, D. (2014). Pomegranate juice consumption increases GSH levels and reduces lipid and protein oxidation in human blood. Food and Chemical Toxicology, 73(August), 1–6. https://doi.org/10.1016/j.fct.2014.07.027

Mertens-Talcott, S. U., Jilma-Stohlawetz, P., Rios, J., Hingorani, L., & Derendorf, H. (2006). Absorption, Metabolism, and Antioxidant Effects of Pomegranate (Punica granatumL.) Polyphenols after Ingestion of a Standardized Extract in Healthy Human Volunteers. Journal of Agricultural and Food Chemistry, 54(23), 8956–8961.

Meyer-Luehmann, M., Spires-Jones, T. L., Prada, C., Garcia-Alloza, M., de Calignon, A., Rozkalne, A., … Hyman, B. T. (2008). Rapid appearance and local toxicity of amyloid-β plaques in a mouse model of Alzheimer's disease. Nature, 451(7179), 720–724. https://doi.org/10.1038/nature06616

Miao, Y., Zhao, S., Gao, Y., Wang, R., Wu, Q., Wu, H., & Luo, T. (2016). Curcumin pretreatment attenuates inflammation and mitochondrial dysfunction in experimental stroke: The possible role of Sirt1 signaling. Brain Research Bulletin, 121, 9–15. https://doi.org/10.1016/j.brainresbull.2015.11.019

Mohsenzadegan, M., & Mirshafiey, A. (2012). The immunopathogenic role of reactive oxygen species in Alzheimer disease. Iran J Allergy Asthma Immunol, 11(3), 203–216. https://doi.org/011.03/ijaai.203216

Moreira, P. I., Carvalho, C., Zhu, X., Smith, M. A., & Perry, G. (2010). Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1802(1), 2–10. https://doi.org/10.1016/j.bbadis.2009.10.006

Morrissette, D. A., Parachikova, A., Green, K. N., & LaFerla, F. M. (2009). Relevance of transgenic mouse models to human Alzheimer disease. The Journal of Biological Chemistry, 284(10), 6033–6037. https://doi.org/10.1074/jbc.R800030200

Morzelle, M. C., Salgado, J. M., Telles, M., Mourelle, D., Bachiega, P., Buck, H. S., & Viel, T. A. (2016). Neuroprotective effects of pomegranate peel extract after chronic infusion with amyloid-?? peptide in mice. PLoS ONE, 11(11), 1–20. https://doi.org/10.1371/journal.pone.0166123

Müller, W. E., Heiser, J., & Leuner, K. (2012). Effects of the standardized Ginkgo biloba extract EGb 761® on neuroplasticity. International Psychogeriatrics / IPA, 24 Suppl 1(1), S21-4. https://doi.org/10.1017/S1041610212000592

Musiek, E. S., & Holtzman, D. M. (2015). Three dimensions of the amyloid hypothesis: time, space and "wingmen." Nat Neurosci, 18(6), 800–806. https://doi.org/10.1038/nn.4018

Musiek, E. S., & Holtzman, D. M. (2016). Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science, 354(6315), 1004–1008. https://doi.org/10.1126/science.aah4968

Nakayama, M., Aihara, M., Chen, Y.-N., Araie, M., Tomita-Yokotani, K., & Iwashina, T. (2011). Neuroprotective effects of flavonoids on hypoxia-, glutamate-, and oxidative stress-induced retinal ganglion cell death. Molecular Vision, 17(July), 1784–1793.

Napryeyenko, O., Sonnik, G., & Tartakovsky, I. (2009). Efficacy and tolerability of Ginkgo biloba extract EGb 761?? by type of dementia: Analyses of a randomised controlled trial. Journal of the Neurological Sciences, 283(1–2), 224–229. https://doi.org/10.1016/j.jns.2009.02.353

Narasingapa, R. B., Jargaval, M. R., Pullabhatla, S., Htoo, H. H., Rao, J. K. S., Hernandez, J. F., … Vincent, B. (2012). Activation of ??-secretase by curcumin-aminoacid conjugates. Biochemical and Biophysical Research Communications, 424(4), 691–696. https://doi.org/10.1016/j.bbrc.2012.07.010

Netzer, W. J., Powell, C., Nong, Y., Blundell, J., Wong, L., Duff, K., … Greengard, P. (2010). Lowering ??-amyloid levels rescues learning and memory in a down

syndrome mouse model. PLoS ONE, 5(6).
https://doi.org/10.1371/journal.pone.0010943

Ng, T. P., Chiam, P. C., Lee, T., Chua, H. C., Lim, L., & Kua, E. H. (2006). Curry consumption and cognitive function in the elderly. American Journal of Epidemiology, 164(9), 898–906. https://doi.org/10.1093/aje/kwj267

Nica Sousa, M., Teixeira, V. H., & Soares, J. (2014). Dietary strategies to recover from exercise-induced muscle damage. Int J Food Sci Nutr, 65(2), 963–7486. https://doi.org/10.3109/09637486.2013.849662

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. The Lancet Neurology, 13(8), 788–794.

Núñez, E., Benito, C., Tolón, R. M., Hillard, C. J., Griffin, W. S. T., & Romero, J. (2008). Glial expression of cannabinoid CB2 receptors and fatty acid amide hydrolase are beta amyloid–linked events in Down's syndrome. Neuroscience, 151(1), 104–110. https://doi.org/10.1016/j.neuroscience.2007.10.029

Ongali, B., Nicolakakis, N., Tong, X.-K., Aboulkassim, T., Papadopoulos, P., Rosa-Neto, P., … Hamel, E. (2014). Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. Neurobiology of Disease, 68, 126–136. https://doi.org/10.1016/j.nbd.2014.04.018

Ono, K., Hamaguchi, T., Naiki, H., & Yamada, M. (2006). Anti-amyloidogenic effects of antioxidants: Implications for the prevention and therapeutics of Alzheimer's disease. Biochimica et Biophysica Acta - Molecular Basis of Disease, 1762(6), 575–586. https://doi.org/10.1016/j.bbadis.2006.03.002

Ono, K., Hasegawa, K., Naiki, H., & Yamada, M. (2004). Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. J Neurosci Res, 75(6), 742–750. Retrieved from http://dx.doi.org/10.1002/jnr.20025

Orgogozo, J. M., Dartigues, J. F., Lafont, S., Letenneur, L., Commenges, D., Salamon, R., … Breteler, M. B. (1997). Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Revue Neurologique, 153(3), 185–192.

Palop, J. J., & Mucke, L. (2010). Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nature Neuroscience, 13(7), 812–818. https://doi.org/10.1038/nn.2583

Papandreou, M. A., Dimakopoulou, A., Linardaki, Z. I., Cordopatis, P., Klimis-Zacas, D., Margarity, M., & Lamari, F. N. (2009). Effect of a polyphenol-rich wild blueberry extract on cognitive performance of mice, brain antioxidant markers and

acetylcholinesterase activity. Behavioural Brain Research, 198(2), 352–358. https://doi.org/10.1016/j.bbr.2008.11.013

Parkar, S. G., Trower, T. M., & Stevenson, D. E. (2013). Fecal microbial metabolism of polyphenols and its effects on human gut microbiota. Anaerobe, 23, 12–19. https://doi.org/10.1016/j.anaerobe.2013.07.009

Parker, J. R. S., Strahler, T. R., Bassett, C. J., Bispham, N. Z., Michel, B., & Seals, D. R. (2016). Curcumin supplementation improves vascular endothelial function in healthy middle - aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress, 9, 1–22. https://doi.org/10.18632/aging.101149

Patten, A. R., Moller, D. J., Graham, J., Gil-Mohapel, J., & Christie, B. R. (2013). Liquid diets reduce cell proliferation but not neurogenesis in the adult rat hippocampus. Neuroscience, 254, 173–184. https://doi.org/10.1016/j.neuroscience.2013.09.024

Peake, J. M., Suzuki, K., & Coombes, J. S. (2007). The influence of antioxidant supplementation on markers of inflammation and the relationship to oxidative stress after exercise. Journal of Nutritional Biochemistry. https://doi.org/10.1016/j.jnutbio.2006.10.005

Perim Baldo, M., Aboussaleh, Y., Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., & Pipingas, A. (2016). Adherence to a Mediterranean-Style Diet and effects on Cognition in Adults: A Qualitative evaluation and Systematic Review of Longitudinal and Prospective Trials. Frontiers in Nutrit, 3(22), 1–13. https://doi.org/10.3389/fnut.2016.00022

Petra, A. I., Panagiotidou, S., Hatziagelaki, E., Stewart, J. M., Conti, P., & Theoharides, T. C. (2015). Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation. Clinical Therapeutics, 37(5), 984–995. https://doi.org/10.1016/j.clinthera.2015.04.002

Pimplikar, S. W. (2009). Reassessing the amyloid cascade hypothesis of Alzheimer's disease. International Journal of Biochemistry and Cell Biology. https://doi.org/10.1016/j.biocel.2008.12.015

Piro, J. R., Benjamin, D. I., Duerr, J. M., Pi, Y., Gonzales, C., Wood, K. M., … Samad, T. A. (2012). A Dysregulated Endocannabinoid-Eicosanoid Network Supports Pathogenesis in a Mouse Model of Alzheimer's Disease. Cell Reports (Vol. 1). https://doi.org/10.1016/j.celrep.2012.05.001

Pistell, P. J., Morrison, C. D., Gupta, S., Knight, A. G., Keller, J. N., Ingram, D. K., & Bruce-Keller, A. J. (2010). Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of Neuroimmunology, 219(1–2), 25–32. https://doi.org/10.1016/j.jneuroim.2009.11.010

Pop, V., Head, E., Hill, M.-A., Gillen, D., Berchtold, N. C., Muggenburg, B. A., … Cotman, C. W. (2010). Synergistic effects of long-term antioxidant diet and behavioral enrichment on beta-amyloid load and non-amyloidogenic processing in aged canines. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 30(29), 9831–9839.

Porquet, D., Griñán-Ferré, C., Ferrer, I., Camins, A., Sanfeliu, C., Del Valle, J., & Pallàs, M. (2014). Neuroprotective role of trans-resveratrol in a murine model of familial Alzheimer's disease. Journal of Alzheimer's Disease : JAD, 42(4), 1209–1220. https://doi.org/10.3233/JAD-140444

Power, S. E., O'Connor, E. M., Ross, R. P., Stanton, C., O'Toole, P. W., Fitzgerald, G. F., & Jeffery, I. B. (2015). Dietary glycaemic load associated with cognitive performance in elderly subjects. European Journal of Nutrition, 54(4), 557–568. https://doi.org/10.1007/s00394-014-0737-5

Pradeep, H., Diya, J. B., Shashikumar, S., & Rajanikant, G. K. (2012). Oxidative stress - Assassin behind the ischemic stroke. Folia Neuropathologica, 50(3), 219–230. https://doi.org/10.5114/fn.2012.30522

Prakash, D., Gopinath, K., & Sudhandiran, G. (2013). Fisetin enhances behavioral performances and attenuates reactive gliosis and inflammation during aluminum chloride-induced neurotoxicity. NeuroMolecular Medicine, 15(1), 192–208. https://doi.org/10.1007/s12017-012-8210-1

Prasanthi, J. R. P., Dasari, B., Marwarha, G., Larson, T., Chen, X., Geiger, J. D., & Ghribi, O. (2010). Caffeine protects against oxidative stress and Alzheimer's disease-like pathology in rabbit hippocampus induced by cholesterol-enriched diet. Free Radical Biology and Medicine, 49(7), 1212–1220. https://doi.org/10.1016/j.freeradbiomed.2010.07.007

Pratheeshkumar, P., Son, Y.-O., Divya, S. P., Roy, R. V., Hitron, J. A., Wang, L., … Shi, X. (2014). Luteolin inhibits Cr(VI)-induced malignant cell transformation of human lung epithelial cells by targeting ROS mediated multiple cell signaling pathways. Toxicology and Applied Pharmacology, 281(2), 230–241. https://doi.org/10.1016/j.taap.2014.10.008

Qu, Z., Mossine, V. V., Cui, J., Sun, G. Y., & Gu, Z. (2016). Protective Effects of AGE and Its Components on Neuroinflammation and Neurodegeneration. NeuroMolecular Medicine, 18(3), 474–482.

Rafii, M. S., Walsh, S., Little, J. T., Behan, K., Reynolds, B., Ward, C., … Alzheimer's Disease Cooperative Study, F. the A. D. C. (2011). A phase II trial of huperzine A in mild to moderate Alzheimer disease. Neurology, 76(16), 1389–1394. https://doi.org/10.1212/WNL.0b013e318216eb7b

Rahman, S., Ansari, R. A., Rehman, H., Parvez, S., & Raisuddin, S. (2011). Nordihydroguaiaretic Acid from Creosote Bush (Larrea tridentata) Mitigates 12-O-Tetradecanoylphorbol-13-Acetate-Induced Inflammatory and Oxidative Stress Responses of Tumor Promotion Cascade in Mouse Skin. Evidence-Based Complementary and Alternative Medicine : ECAM, 2011, 734785. https://doi.org/10.1093/ecam/nep076

Rai, D., Singh, J. K., Roy, N., & Panda, D. (2008). Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. Biochemical Journal, 410(1). Retrieved from http://www.biochemj.org/content/410/1/147

Ramezani, M., Darbandi, N., Khodagholi, F., & Hashemi, A. (2016). Myricetin protects hippocampal CA3 pyramidal neurons and improves learning and memory impairments in rats with Alzheimer's disease. Neural Regeneration Research, 11(12), 1976. https://doi.org/10.4103/1673-5374.197141

Rangel-Ordóñez, L., Nöldner, M., Schubert-Zsilavecz, M., & Wurglics, M. (2010). Plasma levels and distribution of flavonoids in rat brain after single and repeated doses of standardized Ginkgo biloba extract EGb 761®. Planta Medica, 76(15), 1683–1690. https://doi.org/10.1055/s-0030-1249962

Ratia, M., Giménez-Llort, L., Camps, P., Muñoz-Torrero, D., Pérez, B., Clos, M. V., & Badia, A. (2013). Huprine X and huperzine a improve cognition and regulate some neurochemical processes related with Alzheimer's disease in triple transgenic mice (3xTg-AD). Neurodegenerative Diseases, 11(3), 129–140. https://doi.org/10.1159/000336427

Ray, B., Chauhan, N. B., & Lahiri, D. K. (2011). Oxidative insults to neurons and synapse are prevented by aged garlic extract and S-allyl-l-cysteine treatment in the neuronal culture and APP-Tg mouse model. Journal of Neurochemistry, 117(3), 388–402. https://doi.org/10.1111/j.1471-4159.2010.07145.x

Reifert, J., Hartung-Cranston, D., & Feinstein, S. C. (2011). Amyloid ??-mediated cell death of cultured hippocampal neurons reveals extensive Tau fragmentation without increased full-length Tau phosphorylation. Journal of Biological Chemistry, 286(23), 20797–20811. https://doi.org/10.1074/jbc.M111.234674

Reinke, A. A., & Gestwicki, J. E. (2007). Structure–activity Relationships of Amyloid Beta-aggregation Inhibitors Based on Curcumin: Influence of Linker Length and Flexibility. Chemical Biology & Drug Design, 70(3), 206–215. https://doi.org/https://doi.org/10.1111/j.1747-0285.2007.00557.x

Riaz, A., & Khan, R. A. (2016). Anticoagulant, antiplatelet and antianemic effects of Punica granatum (pomegranate) juice in rabbits. Blood Coagulation & Fibrinolysis, 1. https://doi.org/10.1097/MBC.0000000000000415

Ringman, J. M., Frautschy, S. A., Cole, G. M., Masterman, D. L., & Cummings, J. L. (2005). A potential role of the curry spice curcumin in Alzheimer's disease. Current Alzheimer Research, 2(2), 131–136. https://doi.org/10.2174/1567205053585882

Robertson, R. C., Seira Oriach, C., Murphy, K., Moloney, G. M., Cryan, J. F., Dinan, T. G., … Stanton, C. (2016). Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. Brain, Behavior, and Immunity, 59, 21–37. https://doi.org/10.1016/j.bbi.2016.07.145

Rodrigues, J., Assunção, M., Lukoyanov, N., Cardoso, A., Carvalho, F., & Andrade, J. P. (2013). Protective effects of a catechin-rich extract on the hippocampal formation and spatial memory in aging rats. Behavioural Brain Research, 246, 94–102. https://doi.org/10.1016/j.bbr.2013.02.040

Roher, A. E., Palmer, K. C., Yurewicz, E. C., Ball, M. J., & Greenberg, B. D. (1993). Morphological and Biochemical Analyses of Amyloid Plaque Core Proteins Purified from Alzheimer Disease Brain Tissue. Journal of Neurochemistry, 61(5), 1916–1926. https://doi.org/10.1111/j.1471-4159.1993.tb09834.x

Rojanathammanee, L., Puig, K. L., & Combs, C. K. (2013). Pomegranate polyphenols and extract inhibit nuclear factor of activated T-cell activity and microglial activation in vitro and in a transgenic mouse model of Alzheimer disease. The Journal of Nutrition, 143(5), 597–605. https://doi.org/10.3945/jn.112.169516

Rojas, P., Serrano-García, N., Mares-Sámano, J. J., Medina-Campos, O. N., Pedraza-Chaverri, J., & Ögren, S. O. (2008). EGb761 protects against nigrostriatal dopaminergic neurotoxicity in 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-induced Parkinsonism in mice: Role of oxidative stress. European Journal of Neuroscience, 28(1), 41–50. https://doi.org/10.1111/j.1460-9568.2008.06314.x

Rom, O., Korach-Rechtman, H., Hayek, T., Danin-Poleg, Y., Bar, H., Kashi, Y., & Aviram, M. (2016). Acrolein increases macrophage atherogenicity in association with gut microbiota remodeling in atherosclerotic mice: protective role for the polyphenol-rich pomegranate juice. Archives of Toxicology, 1–17. https://doi.org/10.1007/s00204-016-1859-8

Ropacki, S. A., Patel, S. M., & Hartman, R. E. (2013). Pomegranate Supplementation Protects against Memory Dysfunction after Heart Surgery: A Pilot Study. Evidence-Based Complementary and Alternative Medicine, 2013, 932401. https://doi.org/10.1155/2013/932401

Rosen, R. F., Tomidokoro, Y., Farberg, A. S., Dooyema, J., Ciliax, B., Preuss, T. M., … Walker, L. C. (2016). Comparative pathobiology of β-amyloid and the unique susceptibility of humans to Alzheimer's disease. Neurobiology of Aging, 44, 185–196. https://doi.org/10.1016/j.neurobiolaging.2016.04.019

Rosenblat, M., Volkova, N., Coleman, R., & Aviram, M. (2006). Pomegranate byproduct administration to apolipoprotein E-deficient mice attenuates atherosclerosis development as a result of decreased macrophage oxidative stress and reduced cellular uptake of oxidized low-density lipoprotein. Journal of Agricultural and Food Chemistry, 54(5), 1928–1935. https://doi.org/10.1021/jf0528207

Rossi, L., Mazzitelli, S., Arciello, M., Capo, C. R., & Rotilio, G. (2008). Benefits from Dietary Polyphenols for Brain Aging and Alzheimer's Disease. Neurochemical Research, 33(12), 2390–2400. https://doi.org/10.1007/s11064-008-9696-7

Rozenberg, O., Howell, A., & Aviram, M. (2006). Pomegranate juice sugar fraction reduces macrophage oxidative state, whereas white grape juice sugar fraction increases it. Atherosclerosis, 188(1), 68–76. https://doi.org/10.1016/j.atherosclerosis.2005.10.027

Rubio-Perez, J. M., & Morillas-Ruiz, J. M. (2012). A Review: Inflammatory Process in Alzheimer's Disease, Role of Cytokines. The Scientific World Journal, 2012, 1–15. https://doi.org/10.1100/2012/756357

Salomone, S., & Caraci, F. (2012). New pharmacological strategies for treatment of Alzheimer's disease: focus on disease- modifying drugs. British Journal of Clinical Pharmacology. https://doi.org/10.1111/1365-2125.2011.04134.x

Sawmiller, D., Li, S., Shahaduzzaman, M., Smith, A., Obregon, D., Giunta, B., … Tan, J. (2014). Luteolin Reduces Alzheimer's Disease Pathologies Induced by Traumatic Brain Injury. International Journal of Molecular Sciences, 15(1), 895–904. https://doi.org/10.3390/ijms15010895

Schenk, D., Hagen, M., & Seubert, P. (2004). Current progress in beta-amyloid immunotherapy. Current Opinion in Immunology, 16(5), 599–606. https://doi.org/https://doi.org/10.1016/j.coi.2004.07.012

Schindowski, K., Leutner, S., Kressmann, S., Eckert, A., & Müller, W. E. (2001). Age-related increase of oxidative stress-induced apoptosis in mice prevention by Ginkgo biloba extract (EGb761). Journal of Neural Transmission (Vienna, Austria : 1996), 108(8–9), 969–978. https://doi.org/10.1007/s007020170016

Schmitz, C., Rutten, B. P., Pielen, A., Schafer, S., Wirths, O., Tremp, G., … Bayer, T. A. (2004). Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. Am.J.Pathol., 164(0002-9440 (Print)), 1495–1502. https://doi.org/10.1016/S0002-9440(10)63235-X

Schneider, L. S. (2012, October). Ginkgo and AD: Key negatives and lessons from GuidAge. The Lancet Neurology.

Schupf, N., Patel, B., Pang, D., Zigman, W. B., Silverman, W., Mehta, P. D., & Mayeux, R. (2007). Elevated plasma beta-amyloid peptide Abeta(42) levels, incident

dementia, and mortality in Down syndrome. Archives of Neurology, 64(7), 1007–1013. https://doi.org/10.1001/archneur.64.7.1007

Seeram, N. P., Adams, L. S., Henning, S. M., Niu, Y., Zhang, Y., Nair, M. G., & Heber, D. (2005). In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. Journal of Nutritional Biochemistry, 16(6), 360–367. https://doi.org/10.1016/j.jnutbio.2005.01.006

Seeram, N. P., Henning, S. M., Zhang, Y., Suchard, M., Li, Z., & Heber, D. (2006). Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 hours. The Journal of Nutrition, 136(May), 2481–2485.

Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. Science, 298(5594), 789–791. https://doi.org/10.1126/science.1074069

Seong, K. M., Yu, M., Lee, K. S., Park, S., Jin, Y. W., & Min, K. J. (2015). Curcumin mitigates accelerated aging after irradiation in drosophila by reducing oxidative stress. BioMed Research International, 2015. https://doi.org/10.1155/2015/425380

Shafik, N. M., & El Batsh, M. M. (2016). Protective Effects of Combined Selenium and Punica granatum Treatment on Some Inflammatory and Oxidative Stress Markers in Arsenic-Induced Hepatotoxicity in Rats. Biological Trace Element Research, 169(1), 121–128. https://doi.org/10.1007/s12011-015-0397-1

Shipton, O. A., Leitz, J. R., Dworzak, J., Acton, C. E. J., Tunbridge, E. M., Denk, F., … Vargas-Caballero, M. (2011). Tau Protein Is Required for Amyloid β-Induced Impairment of Hippocampal Long-Term Potentiation. The Journal of Neuroscience, 31(5), 1688–1692.

Siemers, E. R., Friedrich, S., Dean, R. A., Gonzales, C. R., Farlow, M. R., Paul, S. M., & DeMattos, R. B. (2010). Safety and Changes in Plasma and Cerebrospinal Fluid Amyloid β After a Single Administration of an Amyloid β Monoclonal Antibody in Subjects With Alzheimer Disease. Clinical Neuropharmacology, 33(2).

Singh, M., Arseneault, M., Sanderson, T., Murthy, V., & Ramassamy, C. (2008). Challenges for Research on Polyphenols from Foods in Alzheimer's Disease: Bioavailability, Metabolism, and Cellular and Molecular Mechanisms. Journal of Agricultural and Food Chemistry, 56(13), 4855–4873. https://doi.org/10.1021/jf0735073

Singh, V., Roth, S., Llovera, G., Sadler, R., Garzetti, D., Stecher, B., … Liesz, A. (2016). Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. Journal of Neuroscience, 36(28).

Sjögren, P., Becker, W., Warensjö, E., Olsson, E., Byberg, L., Gustafsson, I. B., … Cederholm, T. (2010). Mediterranean and carbohydrate-restricted diets and mortality among elderly men: A cohort study in Sweden. American Journal of Clinical Nutrition, 92(4), 967–974. https://doi.org/10.3945/ajcn.2010.29345

Solas, M., Francis, P. T., Franco, R., & Ramirez, M. J. (2013). CB2 receptor and amyloid pathology in frontal cortex of Alzheimer's disease patients. Neurobiology of Aging (Vol. 34). https://doi.org/10.1016/j.neurobiolaging.2012.06.005

Song, C., Shieh, C. H., Wu, Y. S., Kalueff, A., Gaikwad, S., & Su, K. P. (2016, April). The role of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: Acting separately or synergistically? Progress in Lipid Research. https://doi.org/10.1016/j.plipres.2015.12.003

Soscia, S. J., Kirby, J. E., Washicosky, K. J., Tucker, S. M., Ingelsson, M., Hyman, B., … Moir, R. D. (2010). The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide. PLoS ONE, 5(3), e9505. https://doi.org/10.1371/journal.pone.0009505

Sreekumar, S., Sithul, H., Muraleedharan, P., Azeez, J. M., & Sreeharshan, S. (2014). Pomegranate fruit as a rich source of biologically active compounds. BioMed Research International, 2014. https://doi.org/10.1155/2014/686921

Srivareerat, M., Tran, T. T., Salim, S., Aleisa, A. M., & Alkadhi, K. A. (2011). Chronic nicotine restores normal Aβ levels and prevents short-term memory and E-LTP impairment in Aβ rat model of Alzheimer's disease. Neurobiology of Aging, 32(5), 834–844. https://doi.org/10.1016/j.neurobiolaging.2009.04.015

Steele, M., Stuchbury, G., & Münch, G. (2007). The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. Experimental Gerontology, 42(1–2), 28–36. https://doi.org/10.1016/j.exger.2006.06.002

Stranahan, A. M., Cutler, R. G., Button, C., Telljohann, R., & Mattson, M. P. (2011). Diet-induced elevations in serum cholesterol are associated with alterations in hippocampal lipid metabolism and increased oxidative stress. Journal of Neurochemistry, 118(4), 611–615.

Stumm, C., Hiebel, C., Hanstein, R., Purrio, M., Nagel, H., Conrad, A., … Clement, A. B. (2013). Cannabinoid receptor 1 deficiency in a mouse model of Alzheimer's disease leads to enhanced cognitive impairment despite of a reduction in amyloid deposition. Neurobiology of Aging, 34(11), 2574–2584. https://doi.org/10.1016/j.neurobiolaging.2013.05.027

Subash, S., Braidy, N., Essa, M. M., Zayana, A. B., Ragini, V., Al-Adawi, S., … Guillemin, G. J. (2015). Long-term (15mo) dietary supplementation with pomegranates from Oman attenuates cognitive and behavioral deficits in a

transgenic mice model of Alzheimer's disease. Nutrition, 31(1), 223–229. https://doi.org/10.1016/j.nut.2014.06.004

Syed, D. N., Chamcheu, J.-C., Adhami, V. M., & Mukhtar, H. (2013). Pomegranate extracts and cancer prevention: molecular and cellular activities. Anti-Cancer Agents in Medicinal Chemistry, 13(8), 1149–1161. https://doi.org/10.1016/j.biotechadv.2011.08.021.Secreted

Takatsu, H., Owada, K., Abe, K., Nakano, M., & Urano, S. (2009). Effect of vitamin E on learning and memory deficit in aged rats. Journal of Nutritional Science and Vitaminology, 55(5), 389–393. https://doi.org/10.3177/jnsv.55.389

Tavakkoli-Kakhki, M., Motavasselian, M., Mosaddegh, M., Esfahani, M. M., Kamalinejad, M., Nematy, M., & Eslami, S. (2014). Omega-3 and omega-6 content of medicinal foods for depressed patients: implications from the Iranian Traditional Medicine. Avicenna Journal of Phytomedicine, 4(4), 225–230.

Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in transgenic mouse model of Alzheimer's disease. The FASEB Journal, 21(10), 2400–2408. https://doi.org/10.1096/fj.06-7649com

Tendi, E. A., Bosetti, F., DasGupta, S. F., Giuffrida Stella, A. M., Drieu, K., & Rapoport, S. I. (2002). Ginkgo biloba Extracts EGb 761 and Bilobalide Increase NADH Dehydrogenase mRNA Level and Mitochondrial Respiratory Control Ratio in PC12 Cells. Neurochemical Research, 27(4), 319–323. https://doi.org/10.1023/A:1014963313559

Terwel, D., Steffensen, K. R., Verghese, P. B., Kummer, M. P., Gustafsson, J.-Å., Holtzman, D. M., & Heneka, M. T. (2011). Critical role of astroglial apolipoprotein E and liver X receptor-α expression for microglial Aβ phagocytosis. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31(19), 7049–7059.

Thomas, P., Wang, Y. J., Zhong, J. H., Kosaraju, S., O'Callaghan, N. J., Zhou, X. F., & Fenech, M. (2009). Grape seed polyphenols and curcumin reduce genomic instability events in a transgenic mouse model for Alzheimer's disease. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, 661(1–2), 25–34. https://doi.org/10.1016/j.mrfmmm.2008.10.016

Tolón, R. M., Núñez, E., Pazos, M. R., Benito, C., Castillo, A. I., Martínez-Orgado, J. A., & Romero, J. (2009). The activation of cannabinoid CB2 receptors stimulates in situ and in vitro beta-amyloid removal by human macrophages. Brain Research, 1283, 148–154. https://doi.org/10.1016/j.brainres.2009.05.098

Tong, X.-K., Lecrux, C., & Hamel, E. (2012). Age-Dependent Rescue by Simvastatin of Alzheimer's Disease Cerebrovascular and Memory Deficits. Journal of Neuroscience, 32(14), 4705–4715.

Tosun, D., Schuff, N., Mathis, C. A., Jagust, W., Weiner, M. W., & Alzheimer's Disease NeuroImaging Initiative. (2011). Spatial patterns of brain amyloid-beta burden and atrophy rate associations in mild cognitive impairment. Brain : A Journal of Neurology, 134(Pt 4), 1077–1088. https://doi.org/10.1093/brain/awr044

Trichopoulou, A., Martínez-González, M. A., Tong, T. Y., Forouhi, N. G., Khandelwal, S., Prabhakaran, D., … de Lorgeril, M. (2014). Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Medicine, 12, 112. https://doi.org/10.1186/1741-7015-12-112

Uysal, U., Seremet, S., Lamping, J. W., Adams, J. M., Liu, D. Y., Swerdlow, R. H., & Aires, D. J. (2013). Consumption of Polyphenol Plants May Slow Aging and Associated Diseases. Current Pharmaceutical Design, 19(34), 6094–6111. https://doi.org/10.2174/1381612811319340004

Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., de la Torre, R., Martínez-González, M. Á., … Ros, E. (2015). Mediterranean Diet and Age-Related Cognitive Decline. JAMA Internal Medicine, 175(7), 1094. https://doi.org/10.1001/jamainternmed.2015.1668

Vellas, B., Coley, N., Ousset, P. J., Berrut, G., Dartigues, J. F., Dubois, B., … Andrieu, S. (2012). Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. The Lancet Neurology, 11(10), 851–859.

Venkata, C., Prakash, S., & Prakash, I. (2011). Bioactive Chemical Constituents from Pomegranate (Punica granatum) Juice, Seed and Peel-A Review. Int. J. Res. Chem. Environ. International Journal of Research in Chemistry and Environment, 1(1), 1–181.

Vignoli, J. A., Bassoli, D. G., & Benassi, M. T. (2011). Antioxidant activity, polyphenols, caffeine and melanoidins in soluble coffee: The influence of processing conditions and raw material. Food Chemistry, 124(3), 863–868. https://doi.org/10.1016/j.foodchem.2010.07.008

Villemagne, V L, Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., … Masters, C. L. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol, 12(4), 357–367.

Villemagne, Victor L., Pike, K. E., Chételat, G., Ellis, K. A., Mulligan, R. S., Bourgeat, P., … Rowe, C. C. (2011). Longitudinal assessment of Aβ and cognition in aging

and Alzheimer disease. Annals of Neurology, 69(1), 181–192. https://doi.org/10.1002/ana.22248

Vitolo, O., Gong, B., Cao, Z., Ishii, H., Jaracz, S., Nakanishi, K., … Shelanski, M. (2009). Protection against β-amyloid induced abnormal synaptic function and cell death by Ginkgolide J. Neurobiology of Aging, 30(2), 257–265. https://doi.org/10.1016/j.neurobiolaging.2007.05.025

Walsh, D. M., Klyubin, I., Fadeeva, J. V, Cullen, W. K., Anwyl, R., Wolfe, M. S., … Selkoe, D. J. (2002). Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature, 416(6880), 535–539. https://doi.org/10.1038/416535a

Wan, D., Zhou, Y., Wang, K., Hou, Y., Hou, R., & Ye, X. (2016). Resveratrol provides neuroprotection by inhibiting phosphodiesterases and regulating the cAMP/AMPK/SIRT1 pathway after stroke in rats. Brain Research Bulletin, 121, 255–262. https://doi.org/10.1016/j.brainresbull.2016.02.011

Wang, A., Das, P., Switzer, R. C., Golde, T. E., & Jankowsky, J. L. (2011). Robust amyloid clearance in a mouse model of Alzheimer's disease provides novel insights into the mechanism of amyloid-beta immunotherapy. The Journal of Neuroscience, 31(11), 4124–4136.

Wang, D., Ho, L., Faith, J., Ono, K., Janle, E. M., Lachcik, P. J., … Pasinetti, G. M. (2015). Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease ??-amyloid oligomerization. Molecular Nutrition and Food Research, 59(6), 1025–1040. https://doi.org/10.1002/mnfr.201400544

Wang, H., Wang, H., Cheng, H., & Che, Z. (2016). Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Molecular Medicine Reports, 13(5), 4215–4220. https://doi.org/10.3892/mmr.2016.5052

Wang, J., Ho, L., Qin, W., Rocher, A. B., Seror, I., Humala, N., … Pasinetti, G. M. (2005). Caloric restriction attenuates beta-amyloid neuropathology in a mouse model of Alzheimer's disease. The FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology, 19(6), 659–661. https://doi.org/10.1096/fj.04-3182fje

Wang, L., Li, W., Lin, M., Garcia, M., & Mulholland, D. (2013). Luteolin, Ellagic Acid and Punicic Acid are Natural Products that Inhibit Prostate Cancer Metastasis, 0–43.

Wang, R., Ding, Y., Liu, R., Xiang, L., & Du, L. (2010). Pomegranate : Constituents , Bioactivities and Pharmacokinetics. Fruit, Vegetable and Cereal Science and Biotechnology, 4(2), 77–87.

Weinmann, S., Roll, S., Schwarzbach, C., Vauth, C., & Willich, S. N. (2010). Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatrics, 10(1), 14. https://doi.org/10.1186/1471-2318-10-14

West, T., Atzeva, M., & Holtzman, D. M. (2007). Pomegranate polyphenols and resveratrol protect the neonatal brain against hypoxic-ischemic injury. Developmental Neuroscience, 29(4–5), 363–372. https://doi.org/10.1159/000105477

Whyte, A. R., & Williams, C. M. (2015). Effects of a single dose of a flavonoid-rich blueberry drink on memory in 8 to 10y old children. Nutrition, 31(3), 531–534. https://doi.org/10.1016/j.nut.2014.09.013

Wilcock, D. M., Rojiani, A., Rosenthal, A., Subbarao, S., Freeman, M. J., Gordon, M. N., & Morgan, D. (2004). Passive immunotherapy against Aβ in aged APP-transgenic mice reverses cognitive deficits and depletes parenchymal amyloid deposits in spite of increased vascular amyloid and microhemorrhage. Journal of Neuroinflammation, 1(1), 24. https://doi.org/10.1186/1742-2094-1-24

Williams, C. M., El Mohsen, M. A., Vauzour, D., Rendeiro, C., Butler, L. T., Ellis, J. A., … Spencer, J. P. E. (2008). Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. Free Radical Biology and Medicine, 45(3), 295–305. https://doi.org/10.1016/j.freeradbiomed.2008.04.008

Winblad, B., Andreasen, N., Minthon, L., Floesser, A., Imbert, G., Dumortier, T., … Graf, A. (2012). Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study. The Lancet Neurology, 11(7), 597–604. https://doi.org/https://doi.org/10.1016/S1474-4422(12)70140-0

Wirths, O., Multhaup, G., & Bayer, T. A. (2004). A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta-amyloid peptide - the first step of a fatal cascade. Journal of Neurochemistry, 91(3), 513–520. https://doi.org/10.1111/j.1471-4159.2004.02737.x

Wolf, S. A., Bick-Sander, A., Fabel, K., Leal-Galicia, P., Tauber, S., Ramirez-Rodriguez, G., … Kempermann, G. (2010). Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. Cell Communication and Signaling, 8(1), 12. https://doi.org/10.1186/1478-811X-8-12

Wu, J., Bie, B., Yang, H., Xu, J. J., Brown, D. L., & Naguib, M. (2013). Activation of the CB2 receptor system reverses amyloid-induced memory deficiency. Neurobiology of Aging, 34(3), 791–804. https://doi.org/10.1016/j.neurobiolaging.2012.06.011

Xue, Q. S., Sparks, D. L., & Streit, W. J. (2007). Microglial activation in the hippocampus of hypercholesterolemic rabbits occurs independent of increased amyloid production. J Neuroinflammation, 4, 20.

Yan, P., Bero, A. W., Cirrito, J. R., Xiao, Q., Hu, X., Wang, Y., … Lee, J.-M. J.-M. (2009). Characterizing the appearance and growth of amyloid plaques in APP/PS1 mice. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 29(34), 10706–10714.

Yan Xu, Zhang, J., Li Xiong, Lei Zhang, Dong Sun, & Hui Liu. (2010). Green tea polyphenols inhibit cognitive impairment induced by chronic cerebral hypoperfusion via modulating oxidative stress. The Journal of Nutritional Biochemistry, 21(8), 741–748. https://doi.org/10.1016/j.jnutbio.2009.05.002

Yancheva, S., Ihl, R., Nikolova, G., Panayotov, P., Schlaefke, S., & Hoerr, R. (2009). Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. Aging & Mental Health, 13(2), 183–190. https://doi.org/10.1080/13607860902749057

Yang, F., Lim, G. P., Begum, A. N., Ubeda, O. J., Simmons, M. R., Ambegaokar, S. S., … Cole, G. M. (2005). Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. Journal of Biological Chemistry, 280(7), 5892–5901. https://doi.org/10.1074/jbc.M404751200

Yao, Y., Chinnici, C., Tang, H., Trojanowski, J. Q., Lee, V. M., & Praticò, D. (2004). Brain inflammation and oxidative stress in a transgenic mouse model of Alzheimer-like brain amyloidosis. Journal of Neuroinflammation, 1(1), 21. https://doi.org/10.1186/1742-2094-1-21

Yassine, H. N., Rawat, V., Mack, W. J., Quinn, J. F., Yurko-Mauro, K., Bailey-Hall, E., … Schneider, L. S. (2016). The effect of APOE genotype on the delivery of DHA to cerebrospinal fluid in Alzheimer's disease. Alzheimer's Research & Therapy, 8(1), 25. https://doi.org/10.1186/s13195-016-0194-x

Yoshitake, T., Yoshitake, S., & Kehr, J. (2010). The Ginkgo biloba extract EGb 761(R) and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. British Journal of Pharmacology, 159(3), 659–668. https://doi.org/10.1111/j.1476-5381.2009.00580.x

Yu, D., Li, M., Tian, Y., Liu, J., & Shang, J. (2015). Luteolin inhibits ROS-activated MAPK pathway in myocardial ischemia/reperfusion injury. Life Sciences, 122, 15–25. https://doi.org/10.1016/j.lfs.2014.11.014

Yu, T.-X., Zhang, P., Guan, Y., Wang, M., & Zhen, M.-Q. (2015). Protective effects of luteolin against cognitive impairment induced by infusion of Aβ peptide in rats.

International Journal of Clinical and Experimental Pathology, 8(6), 6740–6747. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26261557

Yuan, L., Liu, J., Ma, W., Dong, L., Wang, W., Che, R., & Xiao, R. (2016). Dietary pattern and antioxidants in plasma and erythrocyte in patients with mild cognitive impairment from China. Nutrition, 32(2), 193–198. https://doi.org/10.1016/j.nut.2015.08.004

Yuan, T., Ma, H., Liu, W., Niesen, D. B., Shah, N., Crews, R., … Seeram, N. P. (2016). Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites. ACS Chemical Neuroscience, 7(1), 26–33. https://doi.org/10.1021/acschemneuro.5b00260

Zhang, J.-X., Xing, J.-G., Wang, L.-L., Jiang, H.-L., Guo, S.-L., & Liu, R. (2017). Luteolin Inhibits Fibrillary β-Amyloid1–40-Induced Inflammation in a Human Blood-Brain Barrier Model by Suppressing the p38 MAPK-Mediated NF-κB Signaling Pathways. Molecules, 22(3), 334. https://doi.org/10.3390/molecules22030334

Zhang, Q.-G., Laird, M. D., Han, D., Nguyen, K., Scott, E., Dong, Y., … Brann, D. W. (2012). Critical Role of NADPH Oxidase in Neuronal Oxidative Damage and Microglia Activation following Traumatic Brain Injury. PLoS ONE, 7(4), e34504. https://doi.org/10.1371/journal.pone.0034504

Zhao, X., Strong, R., Piriyawat, P., Palusinski, R., Grotta, J. C., & Aronowski, J. (2010). Caffeinol at the Receptor Level. Stroke, 41(2). Retrieved from http://stroke.ahajournals.org/content/41/2/363.short

Zhao, Y, Dua, P., & Lukiw, W. J. (2015). Microbial Sources of Amyloid and Relevance to Amyloidogenesis and Alzheimer's Disease (AD). Journal of Alzheimer's Disease & Parkinsonism, 5(1), 177. https://doi.org/10.4172/2161-0460.1000177

Zhao, Yuhai, Calon, F., Julien, C., Winkler, J. W., Petasis, N. A., Lukiw, W. J., & Bazan, N. G. (2011). Docosahexaenoic Acid-Derived Neuroprotectin D1 Induces Neuronal Survival via Secretase-and PPARc- Mediated Mechanisms in Alzheimer's Disease Models. PLoS ONE, 6(1). https://doi.org/10.1371/journal.pone.0015816

Zhou, F., Chen, S., Xiong, J., Li, Y., & Qu, L. (2012). Luteolin reduces zinc-induced tau phosphorylation at Ser262/356 in an ROS-dependent manner in SH-SY5Y cells. Biological Trace Element Research, 149(2), 273–279. https://doi.org/10.1007/s12011-012-9411-z

Zimmermann, M., Colciaghi, F., Cattabeni, F., & Di Luca, M. (2002). Ginkgo biloba extract: from molecular mechanisms to the treatment of Alzhelmer's disease.

Cellular and Molecular Biology (Noisy-Le-Grand, France), 48(6), 613–623. Retrieved from http://europepmc.org/abstract/MED/12396071

Zlokovic, B. V. (2008). The Blood-Brain Barrier in Health and Chronic Neurodegenerative Disorders. Neuron, 57(2), 178–201. https://doi.org/10.1016/j.neuron.2008.01.003