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Effects and mechanisms of actions of phytochemicals on Alzheimer's disease neuropathology

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1. ABSTRACT

Alzheimer's disease affects millions of people, yet, there are only a limited number approaches for it pharmacological treatment. Thus, identifying factors that decrease the risk of developing Alzheimer's disease is of paramount importance. A growing body of epidemiological and experimental evidence suggests that dietary fruits and vegetables have neuroprotective effects against the harmful effects of oxidative stress, neuroinflammation, and aging. These effects are mediated by various phytochemical compounds found in plants that exhibit 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 neuropathology and outcomes of Alzheimer's disease. Based on available evidence, we suggest that regular consumption of bioactive phytochemicals from a variety of fruits and vegetables attenuates age- and insult-related neuropathology in Alzheimer's disease.

2. 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 (1, 2). 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.

3. ALZHEIMER'S DISEASE NEUROPATHOLOGY

Recent prevalence rates suggest that over 5 million Americans currently have AD (3), 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 (4-19).

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 (20). Other proteins (e.g., apolipoproteins) and non-proteins (e.g., metals, hemes, and ROS) have also been found within the plaques (21-24). An age related increase in cortical and subcortical amyloid plaque levels is one of the most salient AD biomarkers (25). 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 (20, 26, 27).

Aβ neurotoxicity has been demonstrated in hippocampal cell cultures (28), 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 (29-31). Aβ has also been shown to induce hypersensitivity to excitotoxicity (i.e., damage caused by dysfunctional firing of glutamate) and oxidative stress *in vitro* (32, 33). 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 (34, 35). Importantly, these damaging effects can be ameliorated by dietary antioxidants (36-38). 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 (39, 40). 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 (41, 42).

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 (43-45). 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 (46-48). 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 (49-52). Transgenic rodent models of AD focused on Aβ plaque development appear to mirror the behavioral hallmarks of AD seen in humans diagnosed with AD (53). 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 (54, 55). 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 (56-66), 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. (67, 68).

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 (53, 69-79). Reducing oxidative load in the brain is another pathway to improving cognitive function in Aβ transgenic rodent models without reducing Aβ levels (80-82). 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 (83-86). 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 Aβ 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 Aβ 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 Aβ immunotherapies in transgenic mouse models of AD have yielded promising results, even in the absence of significant reductions in Aβ burden (87-89). Human immunotherapy treatment has been more problematic, due to significant toxicity and tolerability concerns (90-95). Although theses pharmacological failures have raised questions about the amyloid cascade hypothesis of AD, it has also been proposed that Aβ may initiate a multi-faceted pathogenic cascade that causes AD, rather than acting as the sole causative factor (83, 96, 97). These downstream processes include tau aggregation, extracellular senile plaque formations, mitochondrial dysfunction, neuroinflammatory processes, blood brain barrier (BBB) permeability disruption, and gut microbiome disturbances (6, 7, 98-105). 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 (106-109).

4. 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 (110, 111). 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 (112-116). Recent studies of the pharmacokinetic activity of several microbiome-produced polyphenol metabolites found that many of them reached the brain in statistically significant concentrations (105, 114, 117). 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.

4.1. 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 (118). 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 (119). 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 (120).

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 (121). Another study examining the effects of vitamin E supplementation in mild cognitive impairment (MCI) and AD found no evidence that it was beneficial (122). However, one study of older Chinese adults reported that lower α-tocopherol levels were found in those diagnosed with MCI than in healthy controls (123), and another recent study found that higher dietary intake of vitamins A, C, and E is associated with protection from AD (124). 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 (125).

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 (126-130). 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 (131), and several epidemiological studies have demonstrated that diets supplemented with olive oil and/or nuts are associated with improved cognitive function in older adults (127, 132, 133).

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 (134). 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) (135-137).

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 (138). However, recent epidemiological studies have identified smoking as a risk factor for the development of AD (139). 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 4.2.6.2.), 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 Aβ in smoker's brains.

In summary, epidemiological evidence suggests that consuming a wide variety of fruits and vegetables that containing 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.

4.2. Experimental evidence

4.2.1. 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.

4.2.1.1. 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* (140-142). 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 (143-146). Coffee and tea are also discussed in section 4.2.6.1. (caffeine), and tea is discussed in more detail in section 4.2.1.3.1. (flavans).

Diets containing high amounts of the spice mixture curry have been associated with improved cognitive performance in elderly individuals (134, 147). 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(148, 149). In addition to its Aβ binding properties in tissue sections, it has also been demonstrated to prevent and reverse Aβ aggregation *in vitro* (150, 151).

Experimentally, dietary curcumin has been reported to prevent oxidative stress, synaptic damage, cortical microgliosis, and learning deficits in rats after intracerebroventricular infusion of Aβ (152). It also decreased Aβ plaques and oxidative stress in APP transgenic mice (150, 151, 153) and reduced heme-Aβ peroxidase damage to muscarinic ACh receptors (35). 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 (100, 154). 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 (155). 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 (156), 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 (157). Curcumin also inhibits the pro-inflammatory cytokine nuclear transcription factor-κβ (NF-κβ) (158) and modulates other cell-signaling pathways (159) . 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 (150, 160, 161).

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 (162-171). Several animal and human studies have shown that pomegranate juice and extracts demonstrate significant bioactive properties, including antioxidant and anti-inflammatory effects (166, 172-186). 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 (187-189).

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 (190). These results prompted experiments with APP transgenic mice, in which 6 months of consumption reduced Aβ plaques in the hippocampus and improved maze performance (79). 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* (191). 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 (192). These results were similar to other APP transgenic mouse studies in which pomegranate juice supplementation improved learning and memory and reduced Aβ plaque deposition (193) and showed significant improvements in memory, learning, and locomotor function while reducing anxiety (194). Another recent mouse study showed that pomegranate supplementation protected against proton irradiation-induced anxiety (195). Finally, pomegranate supplementation has been experimentally demonstrated to improve cognitive performance in humans after heart surgery (196) and with mild cognitive impairment (197).

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 (185). One study even showed that the conjugated sucroses, fructoses, and glucoses found in pomegranates also have antioxidant properties (183). 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 (166, 198-200). 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 (172, 180-186, 201-209), suggesting that consumption of pomegranates and their juice may protect against AD neuropathology and a several other age-related disease processes.

4.2.1.2. 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 (210). Additionally, resveratrol modulates several Aβ-related cell-signaling pathways (211-213), 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 (214). These findings are supported by resveratrol's neuroprotective effects in adult and neonatal rodent models of ischemic stroke (215, 216).

4.2.1.3. Flavonoids

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

4.2.1.3.1. 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 section 4.2.6.1.). 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 (217, 218) 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 (219).

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 (220). 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 (221). 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 (222). Overall, the phenolic acids and flavonoids found in tea offer multi-faceted neuroprotection from AD via multiple mechanisms.

4.2.1.3.2. Anthocyanidins

Anthocyanidins are water soluble pigments with potent with antioxidant and anti-inflammatory properties found in high concentrations in fruits such as the blueberry (223-225). 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 (226-228). 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 (229).

4.2.1.3.3. 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. (230, 231). Additionally, luteolin has been shown to reduce neuroinflammation and Aβ deposition following experimental traumatic brain injury in transgenic mice (232). Finally, luteolin demonstrates significant antioxidant action, regulates phosphorylation (233, 234), 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 (235-239). 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 (240). 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 (241, 242).

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 4.2.2.1.). 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 (243-245). 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 (246). 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 (243). 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 (247, 248). 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(249), increase production of brain derived neurotrophic factor in aged rats (250), improve mitochondrial respiration *in vitro* (251), and attenuate lipid peroxidation and superoxide free radical production in a mouse model of Parkinson's disease (252) 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 (253). 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 (254). 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 (255). 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 (256). 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 (257, 258).

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 (259). 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.

4.2.2. 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).

4.2.2.1. 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 (257, 258). 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 (260).

4.2.2.2. 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 (261) and protect mitochondria against Aβ deposition by preserving membrane integrity and improving energy metabolism (262). 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 (263, 264). 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 (265).

4.2.2.3. 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 CB_1 and CB_2 cannabinoid receptors. CB_1 receptors are expressed mainly in the cerebral cortex and are thought to be responsible for cannabis' well-documented psychoactive effects. CB_2 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 (266, 267). Additionally, phytocannabinoids have been demonstrated to enhance mitochondrial functioning (268) and stimulate neurogenesis within the embryonic and adult hippocampus (269, 270).

Aging is associated with dysregulation of cannabinoid receptor expression (271), and stimulation of cannabinoid receptors with synthetic cannabinoids has been shown to attenuate these effects (272, 273). A recent study demonstrated that THC restored cognitive performance in older mice, but, interestingly, the opposite effect was observed in younger mice (274). 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 (272). Postmortem studies of AD and Down syndrome brains reveal consistently elevated levels of CB_2 expression, whereas CB_1 receptors are often reduced (275, 276) (277-279). These and other observations suggest that endogenous cannabinoids such as 2-AG mediate inflammatory and neuroprotective processes (280, 281).

A study of transgenic mice that also lacked CB_1 receptors reported that despite a decrease in Aβ plaque load, significant learning and memory deficits persisted, suggesting that that CB_1 receptor deficiency can worsen AD-related cognitive deficits independent of Aβ plaque load (282). 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 (271, 283). Furthermore, another study demonstrated that treatment with a synthetic CB_2 agonist reduced Aβ-induced memory loss (284), and *in vitro* data shows that THC inhibits Aβ aggregation via indirect interaction with Aβ peptides (285). 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 (286-288). 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.

4.2.3. 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 (289-293). SAC has been shown to inhibit and reverse Aβ aggregation *in vitro* and in transgenic mice by binding directly to the Aβ peptide (294). 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 (295, 296). 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.

4.2.4. 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 (297-299). *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 (300). 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 (299). 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 (301). 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 (302, 303).

4.2.5. Phytovitamins

Epidemiological evidence mentioned in section 4.1. 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 (304), 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 (122). However, in a study of aged rats, vitamin E-supplementation improved age-related cognitive deficits (305), 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 (306) along with its associated oxidative stress and neuritic dystrophy (307), and it ameliorated behavioral impairments, oxidative stress, and injury-accelerated Aβ formation resulting from repetitive traumatic brain injury (308). 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 (309). 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 (310). 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 (311). In a study of high dose B vitamin supplements given to healthy adult participants over 4-weeks, increased task-related functional brain activity was reported (312). 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 (313). 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 (314, 315). 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.

4.2.6. Psychoactive alkaloids

4.2.6.1. 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 (316-320). 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 (321). Interestingly, "caffeinol" (a combination of caffeine and ethanol) has been shown to demonstrate potent synergistic neuroprotection in rodent models of stroke (322-324). 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.

4.2.6.2. 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 (325-327). 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 (328, 329). 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 show to inhibit Aβ aggregation by forming permanent covalent bonds with Aβ peptides (330). These finding suggest that pharmaceutical treatment with nicotine may provide positive benefits in the treatment and/or prevention of AD.

5. 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 (331, 332). 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 (76, 194, 333). Furthermore, diets containing a wide variety of bioactive phytochemicals from multiple plant sources may provide synergistic benefits over supplementing with isolated compounds (334, 335). 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.

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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

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