Contents lists available at ScienceDirect

Neurochemistry International

Development of grape polyphenols as multi-targeting strategies for Alzheimer's disease

ARTICLE INFO

Keywords:
Alzheimer disease
Amyloid and tau
Grape polyphenol
Neuroinflammation
Oxidative stress
Synaptic function
Cognitive impairment
Dementia

ABSTRACT

Alzheimer's disease (AD) is by far the most prevalent neurodegenerative disease of aging and is a major burden for patients, caregivers, and the overall health care system. The complexity of AD pathophysiology and the lack of deep understanding of disease mechanisms impeded the development of AD therapy. Currently approved treatments for AD only modestly improve cognitive function but do not modify disease course. The lack of pharmacological approaches has led to the consideration of alternative strategies to prevent or to slow down the progression of AD. There has been a growing interest in the scientific community regarding the impact of diet and nutrition on AD. Grape derived nutraceuticals and phytochemical compounds have demonstrated anti-amyloidogenic, antioxidative, anti-inflammatory and neurotrophic properties and present as potential novel strategies for AD treatment. In this review, we summarize promising grape derived polyphenols that have been shown to modulate AD pathophysiology including amyloid plaques and neurofibrillary tangles formation, AD-induced oxidative stress, neuroinflammation and synaptic dysfunction.

1. Introduction

Alzheimer's disease (AD) is a multifactorial disease characterized by complex relationships between multiple interrelated biological and pathologic processing including genetic and environmental factors, age, education, and lifestyle, which make it difficult to decipher the pathophysiology and consequently challenging to treat or cure. The major hallmarks of AD consist of extracellular accumulation of β-amyloid (Aβ) plaques and intracellular aberrant aggregation of hyperphosphorylated Tau tangles. The accumulation of plaques and neurofibrillary tangles is accompanied by excessive activation of inflammatory pathway, mitochondrial dysfunction, and energy depletion, etc. All these events lead to synaptic loss and neuronal death. These cellular cascade manifest in patients as progressive neurocognitive impairment accompanied by language alterations and continuing deterioration of a person's ability to perform everyday activities (Alzheimer's Association, 2020). Worldwide, approximately 50 million people have AD or AD related dementia but only 25% of people have been properly diagnosed (2019 Alzheimer's Statistics- Alzheimers.net). The number of individuals having AD is projected to double every twenty years (Prince, 2015). Geographically, there is divergence between the countries affected by AD. AD is more prevalent in highly developed countries including Western Europe and North America and is less common in Sub-Saharan Africa (Alzheimer disease international website). In the U. S., AD is by far the most prevalent neurodegenerative disease of aging, with an estimated prevalence of 5.3 million cases, anticipated to grow to 11–16 million cases by the year 2050 ((NASP), 2010, (AA), 2006). Countries with low/middle-income are projected to be significantly affected by 2050. These numbers strongly suggest that the major factors contributing to AD do not solely rely on genetics, age or socio-economical status, other factors such as environmental factors and lifestyle could significantly impact the onset and progression of the disease. AD is a major cause of functional disability in the elderly and pose a heavy burden on the society and the caregivers. Estimated direct healthcare costs due to AD in the U.S. amount to $148 billion annually, plus an additional $94 billion in unpaid costs to caregivers ((NASP), 2010, (AA), 2006). Therefore, as the world aging population continues to grow, the global healthcare system will face major demographic fiscal pressure in coming decades.

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https://doi.org/10.1016/j.neuint.2021.105046
Received 31 July 2020; Received in revised form 11 April 2021; Accepted 12 April 2021
Available online 16 April 2021

2. Multiple pathological mechanisms underlying AD

The pathogenesis of AD is still under active investigation. Histopathologically the familial form of AD and the sporadic forms of AD are indistinguishable from each other and are characterized by neurodegeneration of the brain, especially the hippocampus and the rest of the neocortex that is associated with numerous hyperphosphorylated, aggregated tau in intraneuronal neurofibrillary tangles (NFT) and oligomerized Aβ (oAβ) peptides in extracellular neuritic plaques. Both tau- and Aβ-mediated pathogenic mechanisms are key contributory factors to AD. Moreover, neuroinflammation mediated by primed microglia has increasingly received attention as another key AD pathogenic mechanisms (Agostinho et al., 2010). It is postulated that in the early stage of AD, activation of microglia leads to phagocytosis and reduction of Aβ accumulation. However, prolonged activation of microglia leads to the release of proinflammation cytokines which initiates the inflammatory cascade and subsequently contributes to neuronal damage and cell death (Perry et al., 2010; Streit et al., 2004; Jiang et al., 2012). Oxidative stress and altered redox balance caused by age, AD pathology, metal accumulation and mitochondrial dysfunction also contribute to the pathogenesis of AD. Below, we will discuss the currently knowledge of the factors contributing to AD pathogenesis and the potential processes that can be modulated by select grape derived polyphenols (Fig. 1).

2.1. Beta-amyloid and tau

Senile plaques are mainly composed of Aβ peptides that results from amyloidogenic proteolytic processing of amyloid precursor protein (APP), a transmembrane protein with a large luminal domain and a short cytoplasmic domain (Masters et al., 1985). APP is first cleaved by β-secretase followed by the γ-secretase to generate soluble β-APP (sAPPβ), APP intracellular domain (AICD) and toxic species of Aβ. The non-amyloidogenic processing is initiated by the cleavage of APP by α-secretase within the Aβ domain followed by γ-secretase cleavage resulting in soluble α-APP (sAPPα), AICD and non-toxic P3. Both clinical and preclinical studies showed that cognitive deterioration in AD is linked to the accumulation of extracellular soluble oligomeric Aβ species rather than amyloid plaque deposition in the brain (Morgan, 2005; Shankar et al., 2007, 2008; Selkoe, 2002; Terry et al., 1991; Walsh et al., 2002; Klein, 2002). Oligomeric Aβ, including high molecular weight (HMW) oligomeric Aβ as well as low-n oligomers ranging from dimers to octamers, induce synapse degeneration, synaptic plasticity disruption and decreases in long-term potentiation (LTP) all of which contribute to mechanisms underlying the onset and progression of dementia in AD (Wang et al., 2002; Lacor et al., 2004; Klyubin et al., 2005; Selkoe, 2008; Jacobsen et al., 2006; Lesne et al., 2008; Klein, 2002). It is widely acknowledged that during aging, the imbalance between overproduction of Aβ peptides and their elimination led to the peptide aggregation, and associated neurotoxicity (Kang et al., 1987; Haass et al., 1992; Butterfield et al., 2001; Yankner et al., 1990).

Microtubule-associated protein tau is a highly soluble phosphoprotein that regulates microtubule stability and polymerization (Weingarten et al., 1975; Cleveland et al., 1977). Abnormal aggregation of hyperphosphorylated tau into paired helical filaments (PHFs) and subsequently the formation of neuropil threads (NTs) and neurofibrillary tangles (NFTs) in the brain are characteristic features of AD (Kametani and Hasegawa, 2018). Hyperphosphorylation of tau protein interferes with its normal function (Alonso et al., 1994). In AD, aberrantly phosphorylated tau protein redistributes from the axon to the soma, inducing microtubule network breakdown and axonal transport deficits which ultimately result in neuritic atrophy and cell death. Moreover, hyperphosphorylated tau detached from microtubule is very likely to self-aggregate into neurotoxic PHFs (Mocanu et al., 2008; Anderton et al., 2001). There is a strong association between AD disease progression and tau aggregation and between neuronal loss and the formation of NFTs in the brain (Ihara, 1988).

2.2. Oxidative stress

Oxidative stress is caused by the imbalance between the activity of physiological antioxidant defense system and the production of reactive oxygen species (ROS). Under physiological conditions, the antioxidant defense system will detoxify the organism from the reactive oxygen compounds produced and repair the associated damages (Betteridge, 2000; Dong et al., 2014; M.S. Uddin, 2017). In the brain, ROS are generated from cellular metabolism, and the accumulation of free radicals will interfere with the normal redox (reduction/oxidation) state of the cells and subsequently lead to protein, lipid and DNA damages within the cells. These events will then negatively alter the intracellular signaling pathways, affect brain neurotransmitters and ultimately attack neurons and glial cells, leading to increased cellular apoptosis (Uttara et al., 2009; Gilgun-Sherki et al., 2001; Salganik, 2001). Oxidative stress occurs in several human chronic diseases but has been strongly implicated in aging and neurodegenerative diseases (Salganik, 2001; Fridovich, 1999). Indeed, studies have demonstrated that oxidative stress can lead to the accumulation and aggregation of Aβ in AD patients brains (Botchway Bo, 2017). Studies from postmortem brains revealed age-dependent increase of oxidative damages (oxidized proteins, lipids,

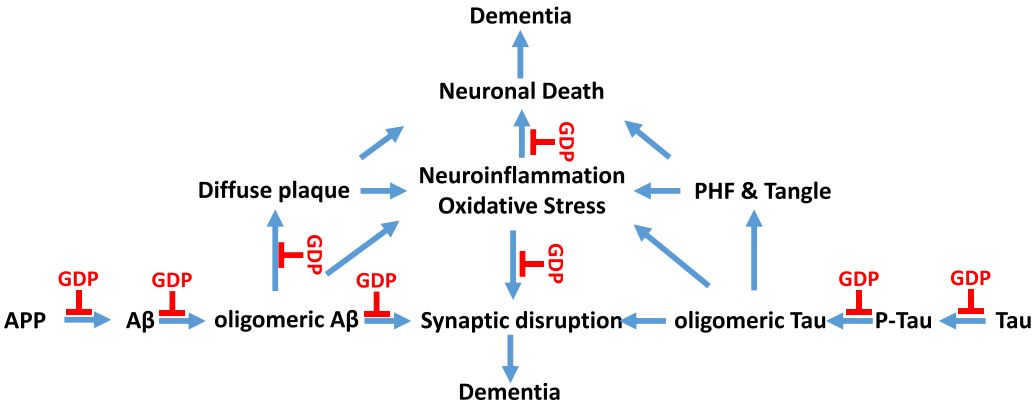

Fig. 1. ***Schematic illustration of the role of grape derived polyphenols (GDP):*** Simplified AD pathogenic pathways (blue arrows) and the protective actions of GDPs (red lines) are schematically illustrated: through 1) interfere with APP process and oAβ induced synaptic disruption; 2) prevent abnormal tau hyperphosphorylation and aberrant aggregation; 3) reduce neuroinflammation and oxidative stress. These collective activities of GDP protect against AD neuropathology by simultaneously targeting multiple AD mechanisms and thereby preventing AD neuropathology and promoting cognition function.

and DNA) (Choi et al., 2004) and mitochondrial dysfunction may contribute to increased oxidative stress in AD (Wang et al., 2009a; Zhu et al., 2004). Oxidative stress may also play a role in protein misfolding contributing to abnormal aggregation of Aβ and tau (MarianI et al., 2005).

2.3. Neuroinflammation

Neuroinflammation, triggered by the innate immune responses in the central nervous system (CNS) plays a central role in AD pathogenesis. This is supported by genome-wide association studies linking microglia-specific genes, *TREM2* and *CD33* and late onset of AD (Guerreiro et al., 2013; Jonsson et al., 2013). Microglial cells are resident macrophage-like cells that play pivotal roles in host defense and tissue repair in the CNS, Normal activities of microglia are considered beneficial in maintaining homeostasis. For example, microglia are involved in the phagocytosis and degradation of abnormal protein aggregates such as Aβ aggregates (Ries and Sastre, 2016; Tahara et al., 2006; Wilkinson and El Khoury, 2012). It has been suggested that failure of microglia to remove Aβ is a key contributing factor of Aβ accumulation (Hickman et al., 2008; Theriault et al., 2015; Weiner and Frenkel, 2006). However, under conditions of chronic neuroinflammation, such as during aging and AD and other neurological disease condition, aberrant chronic activation of microglia leads to disruptions of microenvironment in the CNS (Matcovitch-Natan et al., 2016; Keren-Shaul et al., 2017; Krasemann et al., 2017), thereby contributing to pathogenic insults to the brain. Microglia participate in the immune response in AD by activating the complement cascade and producing inflammatory cytokines such as IL-1β, IL-6 and TNF-α (Wyss-Coray, 2006). IL-6 is one of the main pro-inflammatory cytokines released by activated microglia and - is strongly deregulated in AD (Udan et al., 2008; Sugama et al., 2009; Patel et al., 2005). For example, there is a positive correlation between the degree of mental retardation and serum levels of IL-6 in patients with Down Syndrome whose trisomy for chromosome 21 leads to increased expression of the amyloid precursor protein (APP) and Aβ peptide fragments, leading to AD pathology with clinical symptoms presenting later in life, suggesting that there is a direct relationship between the expression of inflammatory markers and cognitive capacities (Wilcock and Griffin, 2013; Carta et al., 2002).

2.4. Synaptic dysfunction

Synaptic alteration/dysfunction is increasingly viewed as one of the earliest events in the initiation of AD-type cognitive decline preceding neuronal loss (Scheff et al., 2007; Spires et al., 2005; Le et al., 2001). Numerous studies have demonstrated significant alterations in the structure of dendrites and spines, including dystrophic dendrites, aberrant sprouting and curvature of dendritic processes, and loss of dendritic spines with accompanying synapse loss in hippocampal and neocortical pyramidal cells in the brain of AD patients as well as in mouse models of AD (Urbanc et al., 2002; Tsai et al., 2004, Mclean et al., 1999). In both AD patients (Lue et al., 1999; Wang et al., 1999) and AD mouse models (Mucke et al., 2000; Oddo et al., 2003; Shankar et al., 2007; Palop et al., 2006; Davies et al., 1987), losses of brain neuronal synapses and dendritic spines are correlated with increased levels of soluble oAβ in the brain. Most importantly, synaptic loss shows the most robust correlation with cognitive decline in AD (Scheff et al., 2007; Le et al., 2001; Rocher et al., 2008). Therefore, preventing synapse loss and restoring synaptic function may provide a viable strategy for early protection/intervention to slow AD progression and to preserve cognitive function.

3. Challenges for AD therapy and alternative strategy

AD is multifactorial disorder. The familial form of AD accounts for less than 1% of all cases. The exact causes of the sporadic form of AD, which accounts for over 99% of the cases, are not yet well understood. Current FDA-approved treatments for AD include three acetylcholinesterase inhibitors donepezil (ARICEPT, ARICEPT ODT), rivastigmine (EXELON), and galantamine (RAZADYN, REMINYL) (Birks, 2006), and a noncompetitive N-methyl-D-aspartate antagonist, memantine (NAMENDA) (Robinson and Keating, 2006). These medications have been shown to modestly improve cognitive function but do not significantly modify the progression of the disease. Despite tremendous efforts and investment, drug discovery for AD has encountered hundreds of failed clinical trials and there has been no new treatment since the last drug approved in 2003. Current advancement in AD human trials has shown some efficacy of various antibody therapies in removing neuritic plaques: e.g., a phase II study by Eisai and Biogen showed Lecanemab (BAN2401), a humanized IgG1 antibody, significantly reduced amyloid plaques; Donanemab (LY3002813), another humanized IgG1 antibody developed by Eli Lilly showed significant removal of amyloid plaque. Both drugs showed some cognitive stabilization during the trial period but also was associated with increased incidence of amyloid-related imaging abnormalities cerebral edema (ARIA-E). Similar antibody Aducanumab (BIIB037) developed by Biogen was submitted to the FDA but was rejected for its weak efficacy. Therefore, there is an urgent need to develop novel therapeutic strategy to prevent or treat AD.

Alternative treatments for AD have increasingly received attention in the past decade. This is represented by nutraceuticals, including dietary supplements and herbal remedies, acupuncture and meditation. In recent years, nutraceutical research is focused on identifying bioactive components and potential mechanisms underlying their beneficial effects in preventing and potentially treating many diseases. With the increase in life expectancy and health awareness, and market expansion in healthcare spending, nutraceuticals are filling the gaps of the limitation of modern medicine, especially for chronic conditions, such as cardiovascular and neurological disorders. Grape derived nutraceuticals have been receiving increasing attention due to their exceptional biological activities. We will discuss the benefits of grape derived polyphenols in AD-mediated cellular deterioration, including protein misfolding, oxidative stress, inflammation, synaptic dysfunction and memory loss (Fig. 1).

4. Grape polyphenols

Grape and grape derived nutraceutical products are represented by grape seed extract (GSE), grape juice and grape wine. The main nutritional features are mostly associated with their rich content of phenolic acids, flavonoids and stilbenes (Kurkin, 2003). GSE is enriched in proanthocyanidins (PAC) and comprised of the basic flavan-3-ol units including catechin, epicatechin, catechin gallate and epicatechin gallate (Fig. 2A). These basic units form various dimers, trimers, oligmers and polymers though C4→C8 or C4→C6 interflavan bonds (Sharma et al., 2010). Anthocyanins (AC) are pigments that accumulate in berry skins during the ripening of grapes and contribute to the red/blue color of grape juice and grape wine (Cantos et al., 2002; Xu et al., 2011). The major ACs in grape juice and grape wine are cyanidin-glucoside (Glc), delphinidin-Glc, peonidin-Glc, petunidin-Glc and malvidin-Glc (Fig. 2B) (Xu et al., 2011; Rivero-Perez et al., 2008). The content and composition of ACs vary depending on the type of grape berries used and the AC profile in grape juice or grape wine is usually similar to the grape skins. For example, Noiret grape berries is a hybrid predominantly of *Vitis vinifera* and *Vitis labrusca* origin and the most abundant AC in Noiret grape is delphinidin-Glc while the predominant AC in Cabernet Sauvignon grape is malvidin-Glc (Xu et al., 2011; Ryan and Revilla, 2003). The major flavonols in grape juice are myricetin and quercetin and they normally exist as glucosides, galactosides, rhamnosides, rutinosides and glucuronides (Fig. 2C) (Mattivi et al., 2006; Azuma et al., 2012; Koyama et al., 2012; Makris et al., 2006; Castillo-Munoz et al., 2009). Quercetin is the major flavonol of all white grapes while myricetin is the major flavonol of most of the red grapes (Mattivi et al., 2006). The main grape stilbenes are *cis*- and *trans*-resveratrol (3,5,4′-trihydroxysilbene)

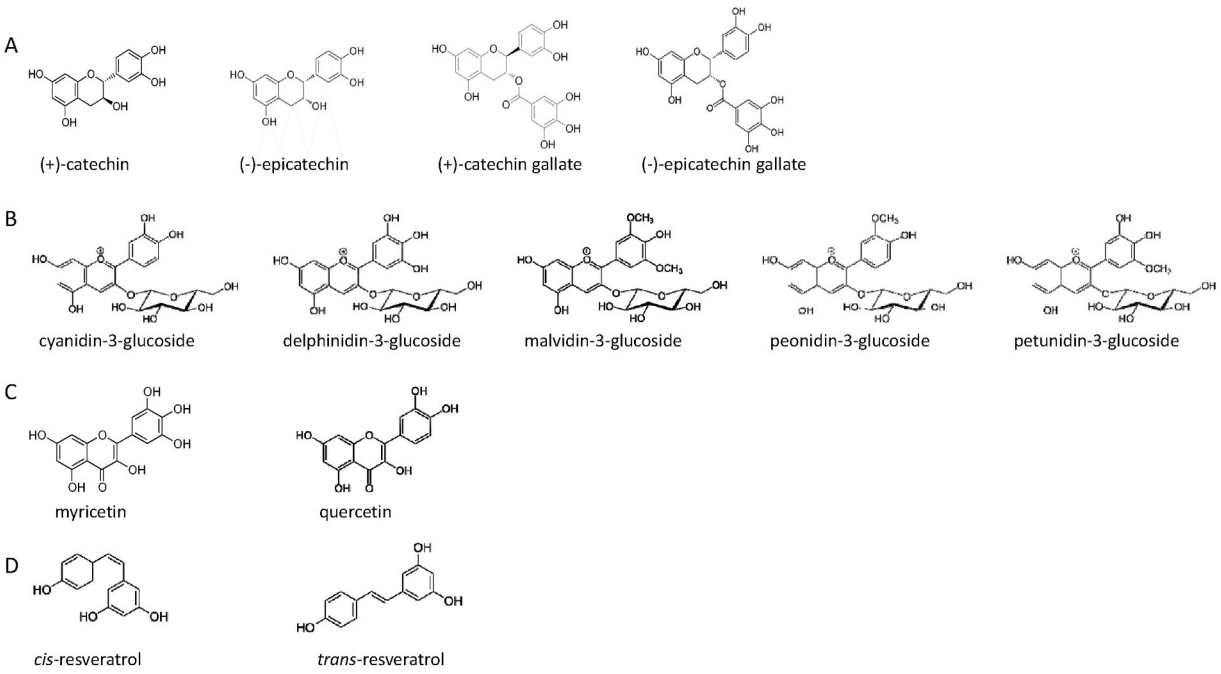

Fig. 2. ***Structures of major polyphenols in grape and grape products.*** (A) Proanthocyanidins (B) Anthocyanins (C) Flavonols and (D) Stilbenes.

(Fig. 2D) and their derivatives (Bavaresco L., 2002, Vitrac et al., 2005). Resveratrol is among the most extensively investigated polyphenols for its pleiotropic activities.

4.1. Grape seed extract (GSE)

There are many commercial grape seed extracts in the market. It is one of the most widely used grape-derived nutraceutical supplements and has been associated with many health benefits. There are growing interests to develop GSE for preventing or treating chronic and degenerative diseases, such as cardiovascular disorders, cancer, as well as neurological diseases including AD. In AD research, GSE has been shown to interfere with Aβ peptides aggregation and potently destabilize preformed misfolded Aβ aggregates *in vitro* (Ono et al., 2008; Hayden et al., 2015; Wang et al., 2008). In animal models, GSE from two commercially available sources (MegaNatural® and Vinlife®) were able to benefit AD pathology in two independent mouse models of AD. Specifically, treatment of Tg2576 mice that overexpress mutant form of APP linked to early-onset familial AD with MegaNatural® GSE (Polyphenolics, CA) significantly reduced Aβ neuropathology and mitigated cognitive deterioration (Wang et al., 2008). Vinlife® GSE obtained from Tarac Technologies (Australia) was shown to reduce amyloid neuropathology in the APPSwe/PS1dE9 mouse model of AD (Wang et al., 2008, 2009b). Research in tauopathy showed that GSE significantly inhibits tau protein aggregation *in vitro* (Ho et al., 2009b) and interferes with the stability of native PHF isolated from AD brain (Ksiezak-Reding et al., 2012). In murine JNPL3 transgenic mice that express human tau containing the most common FTDP-17 mutation, GSE treatment significantly reduced the number of motor neurons containing hyperphosphorylated and insoluble tau in the spinal cord (Santa-Maria et al., 2012). In the TMHT mouse model of AD, GSE treatment significantly attenuated the development of AD type tau neuropathology in the brain through mechanisms associated with attenuation of extracellular signal-receptor kinase (ERK) 1/2 signaling (Wang et al., 2010).

Catechin, epicatechin, catechin gallate and epicatechin gallate are the main PACs in GSE (Fig. 2A) and they exist as monomeric, oligomeric and polyomeric forms. Bioavailability study showed that polymeric forms of PACs are largely not bioavailable (Wang et al., 2012). Monomeric PACs are bioavailable and the primary circulating forms of polyphenols following oral administration of GSE are catechin and epicatechin monomeric glucuronides and methylated glucuronide metabolites. Similar metabolites were identified in the brain following subchronic dosing (Chen et al., 2017; Wang et al., 2013). Oral consumption of epicatechin was shown to inhibit the amyloidogenic APP processing and reduce Aβ neuropathology in vivo in the TASPTM mice that carries the Swedish mutation in APP and the M146V mutation in PSEN1 (Cox et al., 2015). Plant derived epicatechin was also shown to enhance angiogenesis and improve spatial memory in mice (Van Praag et al., 2007). Brain bioavailable epicatechin metabolite 3′-*O*-Me-EC-Gluc was shown to significantly improve basal synaptic transmission and maintenance of long term potentiation (LTP) through mechanisms associated with activation of CREB and CREB co-activator CBP/p300, which are key factors in synaptic plasticity essential for learning and memory (Bartsch et al., 1998; Chrivia et al., 1993). *In vivo* studies also showed that epicatechin can influence ROS and lipid peroxidation in AD-associated oxidative stress. A single oral dose of epicatechin administration was able to decrease Aβ-mediated lipid peroxidation and ROS formation in the hippocampal formation indicating the neuroprotective effects of epicatechin (Cuevas et al., 2009). It is well established that dietary polyphenols can be actively metabolized by intestinal microbiota and convert to phenolic acids. Oral administration of GSE led to the detection of many phenolic acids in plasma. Among these, 3-hydroxybenzoic acid and 3-(3′-hydroxyphenyl) propionic acid were found to accumulate in the brain. *In vitro* assay showed that both phenolic acids can potently inhibit Aβ aggregation into neurotoxic oligomeric and fibrillary forms (Wang et al., 2015).

4.2. Grape juice

Concord grape juice (CGJ) is the most common grape juice in North America. In clinical studies, following a 12-week CGJ supplementation, subjects with mild cognitive impairment (MCI) showed improvements in verbal learning, verbal and spatial recall (Krikorian et al., 2010). MCI subjects with 16 weeks of CGJ consumption reduced semantic interference on memory tasks compared to the placebo group (Krikorian et al., 2012). Brain imaging via functional MRI showed relatively greater activation in anterior and posterior regions of the right hemisphere in subjects with CGJ treatment (Krikorian et al., 2012). In middle-aged and

older adults, 12-week daily consumption of CGJ showed improvements in immediate spatial memory and driving performance compared to the placebo control group and these improvements seems to be long lasting (Lamport et al., 2016). Similar studies were carried out in healthy young adults and consumption of grape juice acutely enhanced aspects of cognition and mood (Haskell-Ramsay et al., 2017). Preclinical studies also showed that grape juice consumption can improve learning and memory in a rat model for AD (Siahmard et al., 2012). Grape juice is a rich source of ACs, PACs, flavonols and phenolic acids. A survey of different grape juice samples showed that the majority of commercial grape juices have similar polyphenol compositions as CGJ (Xu et al., 2011). It is postulated that the rich content of ACs and flavanols in CGJ contribute to its benefits in improving cognitive function. The main ACs in CGJ are cyanidin-Glc, delphinidin-Glc, malvidin-Glc and peonidin-Glc and the major flavonols in CGJ are myricetin-Glc, myricetin-glucuronide (Glur), quercetin-Glc and guercetin-Glur. A survey of 15 different commercial grape juice samples showed that the composition of ACs and flavonols are similar to the CGJ (Xu et al., 2011). Bioavailability studies of CGJ showed that oral administration of CGJ in rats leads to plasma and brain detection of quercetin-Glur, *O*-methyl (Me)-quercetin-Glur, malvidin-Glc, petunidin-Glc, delphinidin-Glc, peonidin-Glc and cyanidin-Glc (Chen et al., 2017; Wang et al., 2013). These brain bioavailable ACs have many bioactivities. ACs are known to be strong antioxidants and anti-inflammatory agents. Oxidative stress and neuroinflammation play important role in the pathogenesis of AD. Delphinidin is a potent lipid peroxidation inhibitor and active scavenger of superoxide anion (Tsuda et al., 1996). The antioxidant capacity of cyanidin-Glc is 3.5 times more potent than vitamin E analogue (Wang et al., 1997) and oral administration of cyanidin-Glc improves oxidative stress-induced hepatic ischemia-reperfusion in rat (Tsuda et al., 2000). Both malvidin-Glc and cyanidin-Glc have potent anti-inflammatory activities. *In vitro* studies demonstrated that malvidin-Glc and cyanidin-Glc are able to decrease inflammatory mediators such as TNF-α, IL-1, IL-6 and iNOS-derived nitric oxide in various cell models (Decendit et al., 2013; Paixao et al., 2012; Serra et al., 2013; Pratheeshkumar et al., 2014). Oligomeric Aβ (oAβ) are potent synaptotoxins and can impair synaptic plasticity. Hippocampal slices from young mice exhibit impaired LTP following oAβ incubation while cyanidin-Glc was able to protect against oAβ-induced synaptic deficits (Wang et al., 2014).

4.3. Grape wine

Epidemiological studies indicate that moderate consumption of red wine lower the incidence of AD (Dartigues et al., 1993; Orgogozo et al., 1997; Dorozynski, 1997; Luchsinger et al., 2004; Truelsen et al., 2002). In preclinical studies, it has been shown that consumption of Cabernet Sauvignon and Muscadine wine significantly reduced AD-type neuropathology and improved cognitive function in Tg2576 mouse model of AD (Wang et al., 2006; Ho et al., 2009a). Interestingly, the two red wines attenuate AD phenotypes through independent mechanisms. In particular, Cabernet Sauvignon promotes non-amyloidogenic processing of APP (Wang et al., 2006) while Muscadine interferes with Aβ oligomerization (Ho et al., 2009a). Bioavailability studies showed that flavonal quercetin-3-O-Glur is capable of reaching the brain following oral wine consumption and contributes to protection against AD by modulating multiple mechanisms, including reducing Aβ generation, reducing Aβ oligomerization, and promoting neuroplasticity processes (Ho et al., 2013). Quercetin is a flavonoid mainly found in red wine, but can also be found in onions and apples (Priprem et al., 2008). It was shown to be able to reduce brain $A\beta_{40}$ and $A\beta_{42}$ levels by preventing APP cleavage by BACE-1 in a 3xTg mouse model for AD (Sabogal-Guaqueta et al., 2015). Treatment with quercetin was shown to modulate both soluble and insoluble Aβ levels in the brain (Sabogal-Guaqueta et al., 2015; Moreno et al., 2017; Zaplatic et al., 2019), and promotes learning and memory functions (Devi and Ohno, 2012; Spencer, 2009). Moreover, quercetin has been shown to be more effective than Vitamin C and E, glutathione or beta carotene (Choi et al., 2003; Heijnen et al., 2002; Rice-Evans et al., 1995) at scavenging free radicals and preventing oxidant-induced apoptosis. In addition to its high oxygen radical scavenging properties, quercetin also has the ability to inhibit lipid peroxidation (FioranI et al., 2010) and to chelate iron and other metals that could be detrimental to the brain (Salganik, 2001; Rice-Evans et al., 1995).

Resveratrol is the main stilbene found in grape skin and red wines. The health benefits of resveratrol have been intensively investigated in various diseases due to its antioxidant, anti-inflammation and neuroprotective activities. It has been reported that resveratrol could modulate neuroinflammation and induce adaptive immunity in patients with AD (Moussa et al., 2017). Subjects with mild-moderate AD were treated orally with pure, synthetic resveratrol at 500 mg once a day with a dose escalation of 500 mg every 13 weeks. In AD subject following 52-weeks treatment, there was a significant decrease of CSF level of MMP9, a metallopeptidase that regulates BBB permeability. The decrease of CSF MMP9 levels suggests that resveratrol may decrease the permeability of CNS and reduce the infiltration of leukocytes and other immune modulators into the brain. Treatment with resveratrol was also accompanied by reduced levels of pro-inflammatory cytokines and chemokines such as IL-IR4, IL-12P40, IL-12P70, TNF-α and RANTES in plasma. Interestingly, resveratrol treatment also increased CSF level of macrophage-derived chemokine (MDC) (Moussa et al., 2017), a potent chemoattractant for immature dendritic cells and monocytes (Godiska et al., 1997), suggesting resveratrol treatment may promote immune responses to amyloid-induced brain injury. In animal models, resveratrol was shown to promote intracellular Aβ clearance through activation of autophagy and AMPK signaling (Vingtdeux et al., 2011). In tau transgenic mice, resveratrol was shown to inhibit tau aggregation and reduce tau pathology (Anderson et al., 1979; Yu et al., 2018). The anti-inflammatory activity of resveratrol is mediated through NF-κB. Resveratrol dose-dependently inhibits IKKα, IκBα, and NF-κB activation *in vitro* (Capiralla et al., 2012; Zhao et al., 2018) and suppress NF-κB in vivo (Capiralla et al., 2012; Poulose et al., 2015). Resveratrol can modulate oxidative stress through induction of nuclear factor erythroid 2-related factor (Nrf2)-dependent heme oxygenase 1 (HO-1) expression (Kim et al., 2012; Son et al., 2013). In animal studies, resveratrol treatment significantly increases superoxide dismutase enzyme activity (Chen et al., 2016). The neuroprotective effect of resveratrol is thought to be mediated by SIRT1, a NAD + -dependent deacetylase responsible for regulating brain senescence (Herskovits and Guarente, 2014; Stacchiotti et al., 2018). Overexpression of SIRT1 in mice reduces brain inflammation, and SIRT1 deficiency exacerbated Aβ-mediated pathology in mice (Pasinetti et al., 2015). It is worth mentioning that despite its exceptional bioactivities, clinical trials in AD prevention and treatment are largely unsuccessful. This could be due to the low bioavailability and fast metabolism of resveratrol in the intestine and liver (Sergides et al., 2016). In animal studies, oral gavaging of 300 mg/kg/day trans-resveratrol for 10 days led to the detection of less than 1 nM of resveratrol-3-O-glur in the brain (Wang et al., 2014; Chen et al., 2017) further confirming that brain bioavailability of resveratrol is very limited.

Similarly to GSE, wine polyphenols are also extensively metabolized by intestinal microbiota to various phenolic metabolites and may exert their bioactivity to brain health.

5. Conclusion

Grape and grape derived nutraceutical products from grape juice and wine are continuously receiving increasing attention. Preclinical evidence demonstrated that grape polyphenols attenuate Aβ-mediated neuropathology by directly inhibiting Aβ generation, promoting Aβ clearance and interfering with Aβ oligomerization. Grape polyphenols may mitigate tau-mediated neuropathology thorough modulating tau hyperphosphorylation and inhibiting aberrant tau aggregation. Through their strong antioxidant, anti-inflammatory activities, grape

polyphenols exert neuroprotection and promote brain resilience to AD and related dementia (Fig. 1).

In spite of their promising bioactivities and increasing efforts committed to clinical testing of polyphenols for AD intervention, clinical development of grape polyphenols for AD is hindered by our limited knowledge of 1) Bioavailability: the specific forms of polyphenols (including polyphenol metabolites) that are capable of accumulating in the brain. Most polyphenols are hydrophilic and penetrate cellular lipid bilayers by passive diffusion, and in most cases, membrane carriers are required to transport polyphenol metabolites across the gastrointestinal track, the blood-brain barrier (BBB), and cellular plasma membrane. 2) Bioactivities: the specific brain-available polyphenol forms that engage in AD target molecules and their underlying mechanisms of actions. AD is a multifactorial disease, involving several different major etiopathogenic processes. It is currently thought that the lackluster performance of preclinical paradigms and concepts for developing AD therapies might be in part, due to the inadequacy of the prevailing approach targeting individual instead of multiple AD pathogenic mechanisms. Grape polyphenols have shown pleotropic bioactivities. Conceptually, grape polyphenols can be designed to target multiple AD pathogenic mechanisms and increase the likelihood of therapeutic efficacy. Therefore, understanding the molecular mechanisms of action will provide bases for the development of grape polyphenols as a multi-target AD intervention. 3) Standardization: the composition of most of the crude extracts such as grape seed polyphenol extracts, grape juice or wine extracts is very complicated and varies from batch to batch, which limits their advance in clinical studies. Therefore, standardization of grape derived products is an important aspect for their future development as AD therapies.

In summary, grape derived nutraceutical products have shown promising health benefits. However, the path to further advancement on AD treatment remains long and more scientific investigation are needed to fill the fundamental gaps for future translational studies.

Funding

Funding was provided by the P50 AT008661-01 from the National Center for Complementary and Integrative Health (NCCIH) and the Office of Dietary Supplements (ODS). In addition, J.W. holds positions in the Research and Development unit of the Basic and Biomedical Research and Training Program at the James J. Peters Veterans Affairs Medical Center.

Author statement

Farida El Gaamouch: Conceptualization, writing-original draft preparation, Kalena Liu: writing-original draft preparation. Hsiao-yun Lin: writing-original draft preparation. Clark Wu: writing-original draft preparation. Jun Wang: Conceptualization, writing-original draft, writing-review & editing.

Declaration of competing interest

Authors declare no conflict of interest.

References

Aa, A.A., 2006. Fact Sheet: Alzheimer's Disease. Association, A.s.
Agostinho, P., Cunha, R.A., Oliveira, C., 2010. Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. Curr. Pharmaceut. Des. 16, 2766–2778.
Alonso, A.C., Zaidi, T., Grundke-Iqbal, I., Iqbal, K., 1994. Role of abnormally phosphorylated tau in the breakdown of microtubules in Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 91, 5562–5566.
2020 Alzheimer's Association, 2020. Alzheimer's disease facts and figures. Alzheimers Dement 16 (3), 391–460.
Anderson, A.O., Anderson, N.D., White, J.D., 1979. Basic mechanisms of lymphocyte recirculation in Lewis rats. Adv. Exp. Med. Biol. 114, 73–83.
Anderton, B.H., Betts, J., Blackstock, W.P., Brion, J.P., Chapman, S., Connell, J., Dayanandan, R., Gallo, J.M., Gibb, G., Hanger, D.P., Hutton, M., Kardalinou, E., Leroy, K., Lovestone, S., Mack, T., Reynolds, C.H., Van Slegtenhorst, M., 2001. Sites of phosphorylation in tau and factors affecting their regulation. Biochem. Soc. Symp. 73–80.
Azuma, A., Yakushiji, H., Koshita, Y., Kobayashi, S., 2012. Flavonoid biosynthesis-related genes in grape skin are differentially regulated by temperature and light conditions. Planta 236, 1067–1080.
Bartsch, D., Casadio, A., Karl, K.A., Serodio, P., Kandel, E.R., 1998. CREB1 encodes a nuclear activator, a repressor, and a cytoplasmic modulator that form a regulatory unit critical for long-term facilitation. Cell 95, 211–223.
Bavaresco, L., F, M., Trevisan, M., Mattivi, F., Vrhovsek, U., Falchetti, R., 2002. The occurrence of the stilbene piceatannol in grapes. Journal of Grapevine Research. Vitis 41, 133–136.
Betteridge, D.J., 2000. What is oxidative stress? Metabolism 49, 3–8.
Birks, J., 2006. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst. Rev. CD005593.
Botchway Bo, I.I., 2017. Alzheimer's disease – the past, the present and the future. Sci. J. Clin. Med. 6 (1), 1–19.
Butterfield, D.A., Drake, J., Pocernich, C., Castegna, A., 2001. Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide. Trends Mol. Med. 7, 548–554.
Cantos, E., Espin, J.C., Tomas-Barberan, F.A., 2002. Varietal differences among the polyphenol profiles of seven table grape cultivars studied by LC-DAD-MS-MS. J. Agric. Food Chem. 50, 5691–5696.
Capiralla, H., Vingtdeux, V., Zhao, H., Sankowski, R., Al-Abed, Y., Davies, P., Marambaud, P., 2012. Resveratrol mitigates lipopolysaccharide- and Abeta-mediated microglial inflammation by inhibiting the TLR4/NF-kappaB/STAT signaling cascade. J. Neurochem. 120, 461–472.
Carta, M.G., Serra, P., Ghiani, A., Manca, E., Hardoy, M.C., Del Giacco, G.S., Diaz, G., Carpiniello, B., Manconi, P.E., 2002. Chemokines and pro-inflammatory cytokines in Down's syndrome: an early marker for Alzheimer-type dementia? Psychother. Psychosom. 71, 233–236.
Castillo-Munoz, N., Gomez-Alonso, S., Garcia-Romero, E., Gomez, M.V., Velders, A.H., Hermosin-Gutierrez, I., 2009. Flavonol 3-O-glycosides series of Vitis vinifera Cv. Petit Verdot red wine grapes. J. Agric. Food Chem. 57, 209–219.
Chen, W.M., Shaw, L.H., Chang, P.J., Tung, S.Y., Chang, T.S., Shen, C.H., Hsieh, Y.Y., Wei, K.L., 2016. Hepatoprotective effect of resveratrol against ethanol-induced oxidative stress through induction of superoxide dismutase in vivo and in vitro. Exp Ther Med 11, 1231–1238.
Chen, T.Y., Ferruzzi, M.G., Wu, Q.L., Simon, J.E., Talcott, S.T., Wang, J., Ho, L., Todd, G., Cooper, B., Pasinetti, G.M., Janle, E.M., 2017. Influence of diabetes on plasma pharmacokinetics and brain bioavailability of grape polyphenols and their phase II metabolites in the Zucker diabetic fatty rat. Mol. Nutr. Food Res. 61.
Choi, Y.J., Kang, J.S., Park, J.H., Lee, Y.J., Choi, J.S., Kang, Y.H., 2003. Polyphenolic flavonoids differ in their antiapoptotic efficacy in hydrogen peroxide-treated human vascular endothelial cells. J. Nutr. 133, 985–991.
Choi, J., Levey, A.I., Weintraub, S.T., Rees, H.D., Gearing, M., Chin, L.S., Li, L., 2004. Oxidative modifications and down-regulation of ubiquitin carboxyl-terminal hydrolase L1 associated with idiopathic Parkinson's and Alzheimer's diseases. J. Biol. Chem. 279, 13256–13264.
Chrivia, J.C., Kwok, R.P., Lamb, N., Hagiwara, M., Montminy, M.R., Goodman, R.H., 1993. Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature 365, 855–859.
Cleveland, D.W., Hwo, S.Y., Kirschner, M.W., 1977. Purification of tau, a microtubule-associated protein that induces assembly of microtubules from purified tubulin. J. Mol. Biol. 116, 207–225.
Cox, C.J., Choudhry, F., Peacey, E., Perkinton, M.S., Richardson, J.C., Howlett, D.R., Lichtenthaler, S.F., Francis, P.T., Williams, R.J., 2015. Dietary (-)-epicatechin as a potent inhibitor of betagamma-secretase amyloid precursor protein processing. Neurobiol. Aging 36, 178–187.
Cuevas, E., Limon, D., Perez-Severiano, F., Diaz, A., Ortega, L., Zenteno, E., Guevara, J., 2009. Antioxidant effects of epicatechin on the hippocampal toxicity caused by amyloid-beta 25-35 in rats. Eur. J. Pharmacol. 616, 122–127.
Dartigues, J.F., Orgogozo, J.M., Letenneur, L., Barberger-Gateau, P., 1993. [French epidemiological bases for the treatment of dementia syndromes and cognitive impairment in the elderly]. Therapie 48, 185–187.
Davies, C.A., Mann, D.M., Sumpter, P.Q., Yates, P.O., 1987. A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. J. Neurol. Sci. 78, 151–164.
Decendit, A., Mamani-Matsuda, M., Aumont, V., Waffo-Teguo, P., Moynet, D., Boniface, K., Richard, E., Krisa, S., Rambert, J., Merillon, J.M., Mossalayi, M.D., 2013. Malvidin-3-O-beta glucoside, major grape anthocyanin, inhibits human macrophage-derived inflammatory mediators and decreases clinical scores in arthritic rats. Biochem. Pharmacol. 86, 1461–1467.
Devi, L., Ohno, M., 2012. 7,8-dihydroxyflavone, a small-molecule TrkB agonist, reverses memory deficits and BACE1 elevation in a mouse model of Alzheimer's disease. Neuropsychopharmacology 37, 434–444.
Dong, Y.S., Wang, J.L., Feng, D.Y., Qin, H.Z., Wen, H., Yin, Z.M., Gao, G.D., Li, C., 2014. Protective effect of quercetin against oxidative stress and brain edema in an experimental rat model of subarachnoid hemorrhage. Int. J. Med. Sci. 11, 282–290.
Dorozynski, A., 1997. Wine may prevent dementia. BMJ 314, 997.
FioranI, M., Guidarelli, A., Blasa, M., Azzolini, C., Candiracci, M., Piatti, E., Cantoni, O., 2010. Mitochondria accumulate large amounts of quercetin: prevention of mitochondrial damage and release upon oxidation of the extramitochondrial fraction of the flavonoid. J. Nutr. Biochem. 21, 397–404.

Fridovich, I., 1999. Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? Ann. N. Y. Acad. Sci. 893, 13–18.
Gilgun-Sherki, Y., Melamed, E., Offen, D., 2001. Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. Neuropharmacology 40, 959–975.
Godiska, R., Chantry, D., Raport, C.J., Sozzani, S., Allavena, P., Leviten, D., Mantovani, A., Gray, P.W., 1997. Human macrophage-derived chemokine (MDC), a novel chemoattractant for monocytes, monocyte-derived dendritic cells, and natural killer cells. J. Exp. Med. 185, 1595–1604.
Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J.S., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J.C., Amouyel, P., Goate, A., Rademakers, R., Morgan, K., Powell, J., St George-Hyslop, P., Singleton, A., Hardy, J., Alzheimer Genetic Analysis, G, 2013. TREM2 variants in Alzheimer's disease. N. Engl. J. Med. 368, 117–127.
Haass, C., Schlossmacher, M.G., Hung, A.Y., Vigo-Pelfrey, C., Mellon, A., Ostaszewski, B. L., Lieberburg, I., Koo, E.H., Schenk, D., Teplow, D.B., et al., 1992. Amyloid beta-peptide is produced by cultured cells during normal metabolism. Nature 359, 322–325.
Haskell-Ramsay, C.F., Stuart, R.C., Okello, E.J., Watson, A.W., 2017. Cognitive and mood improvements following acute supplementation with purple grape juice in healthy young adults. Eur. J. Nutr. 56, 2621–2631.
Hayden, E.Y., Yamin, G., Beroukhim, S., Chen, B., Kibalchenko, M., Jiang, L., Ho, L., Wang, J., Pasinetti, G.M., Teplow, D.B., 2015. Inhibiting amyloid beta-protein assembly: size-activity relationships among grape seed-derived polyphenols. J. Neurochem. 135, 416–430.
Heijnen, C.G., Haenen, G.R., Oostveen, R.M., Stalpers, E.M., Bast, A., 2002. Protection of flavonoids against lipid peroxidation: the structure activity relationship revisited. Free Radic. Res. 36, 575–581.
Herskovits, A.Z., Guarente, L., 2014. SIRT1 in neurodevelopment and brain senescence. Neuron 81, 471–483.
Hickman, S.E., Allison, E.K., El Khoury, J., 2008. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. J. Neurosci. 28, 8354–8360.
Ho, L., Chen, L.H., Wang, J., Zhao, W., Talcott, S.T., Ono, K., Teplow, D., Humala, N., Cheng, A., Percival, S.S., Ferruzzi, M., Janle, E., Dickstein, D.L., Pasinetti, G.M., 2009a. Heterogeneity in red wine polyphenolic contents differentially influences Alzheimer's disease-type neuropathology and cognitive deterioration. J Alzheimers Dis 16, 59–72.
Ho, L., Yemul, S., Wang, J., Pasinetti, G.M., 2009b. Grape seed polyphenolic extract as a potential novel therapeutic agent in tauopathies. J Alzheimers Dis 16, 433–439.
Ho, L., Ferruzzi, M.G., Janle, E.M., Wang, J., Gong, B., Chen, T.Y., Lobo, J., Cooper, B., Wu, Q.L., Talcott, S.T., Percival, S.S., Simon, J.E., Pasinetti, G.M., 2013. Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. Faseb. J. 27, 769–781.
Ihara, Y., 1988. Massive somatodendritic sprouting of cortical neurons in Alzheimer's disease. Brain Res. 459, 138–144.
Jacobsen, J.S., Wu, C.C., Redwine, J.M., Comery, T.A., Arias, R., Bowlby, M., Martone, R., Morrison, J.H., Pangalos, M.N., Reinhart, P.H., Bloom, F.E., 2006. Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 103, 5161–5166.
Jiang, T., Yu, J.T., Tan, L., 2012. Novel disease-modifying therapies for Alzheimer's disease. J Alzheimers Dis 31, 475–492.
Jonsson, T., Stefansson, H., Steinberg, S., Jonsdottir, I., Jonsson, P.V., Snaedal, J., Bjornsson, S., Huttenlocher, J., Levey, A.I., Lah, J.J., Rujescu, D., Hampel, H., Giegling, I., Andreassen, O.A., Engedal, K., Ulstein, I., Djurovic, S., Ibrahim-Verbaas, C., Hofman, A., Ikram, M.A., Van Duijn, C.M., Thorsteinsdottir, U., Kong, A., Stefansson, K., 2013. Variant of TREM2 associated with the risk of Alzheimer's disease. N. Engl. J. Med. 368, 107–116.
Kametani, F., Hasegawa, M., 2018. Reconsideration of amyloid hypothesis and tau hypothesis in alzheimer's disease. Front. Neurosci. 12, 25.
Kang, J., Lemaire, H.G., Unterbeck, A., Salbaum, J.M., Masters, C.L., Grzeschik, K.H., Multhaup, G., Beyreuther, K., Muller-Hill, B., 1987. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 325, 733–736.
Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T.K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M., Amit, I., 2017. A unique microglia type Associated with restricting development of alzheimer's disease. Cell 169, 1276–1290 e17.
Kim, D.W., Kim, Y.M., Kang, S.D., Han, Y.M., Pae, H.O., 2012. Effects of resveratrol and trans-3,5,4'-trimethoxystilbene on glutamate-induced cytotoxicity, heme oxygenase-1, and sirtuin 1 in HT22 neuronal cells. Biomol Ther (Seoul) 20, 306–312.
Klein, W.L., 2002. Abeta toxicity in Alzheimer's disease: globular oligomers (ADDLs) as new vaccine and drug targets. Neurochem. Int. 41, 345–352.
Klyubin, I., Walsh, D.M., Lemere, C.A., Cullen, W.K., Shankar, G.M., Betts, V., Spooner, E. T., Jiang, L., Anwyl, R., Selkoe, D.J., Rowan, M.J., 2005. Amyloid beta protein immunotherapy neutralizes Abeta oligomers that disrupt synaptic plasticity in vivo. Nat. Med. 11, 556–561.
Koyama, K., Ikeda, H., Poudel, P.R., Goto-Yamamoto, N., 2012. Light quality affects flavonoid biosynthesis in young berries of Cabernet Sauvignon grape. Phytochemistry 78, 54–64.
Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., BeckerS, L., O'loughlin, E., Xu, Y., Fanek, Z., Greco, D.J., Smith, S.T., Tweet, G., Humulock, Z., Zrzavy, T., Conde-Sanroman, P., Gacias, M., Weng, Z., Chen, H., Tjon, E., Mazaheri, F., Hartmann, K., Madi, A., Ulrich, J.D., Glatzel, M., Worthmann, A., Heeren, J., Budnik, B., Lemere, C., Ikezu, T., Heppner, F.L., Litvak, V., Holtzman, D.M., Lassmann, H., Weiner, H.L., Ochando, J., Haass, C., Butovsky, O., 2017. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity 47, 566–581 e9.
Krikorian, R., Nash, T.A., Shidler, M.D., Shukitt-Hale, B., Joseph, J.A., 2010. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br. J. Nutr. 103, 730–734.
Krikorian, R., Boespflug, E.L., Fleck, D.E., Stein, A.L., Wightman, J.D., Shidler, M.D., Sadat-Hossieny, S., 2012. Concord grape juice supplementation and neurocognitive function in human aging. J. Agric. Food Chem. 60, 5736–5742.
Ksiezak-Reding, H., Ho, L., Santa-Maria, I., Diaz-Ruiz, C., Wang, J., Pasinetti, G.M., 2012. Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. Neurobiol. Aging 33, 1427–1439.
Kurkin, V.A., 2003. Phenylpropanoids from medicinal plants: distribution, classification, structural analysis, and biological activity. Chem. Nat. Compd. 39, 123–153.
Lacor, P.N., Buniel, M.C., Chang, L., Fernandez, S.J., Gong, Y., Viola, K.L., Lambert, M.P., Velasco, P.T., Bigio, E.H., Finch, C.E., Krafft, G.A., Klein, W.L., 2004. Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J. Neurosci. 24, 10191–10200.
Lamport, D.J., Lawton, C.L., Merat, N., Jamson, H., Myrissa, K., Hofman, D., Chadwick, H.K., Quadt, F., Wightman, J.D., Dye, L., 2016. Concord grape juice, cognitive function, and driving performance: a 12-wk, placebo-controlled, randomized crossover trial in mothers of preteen children. Am. J. Clin. Nutr. 103, 775–783.
Le, R., Cruz, L., Urbanc, B., KnowleS, R.B., Hsiao-Ashe, K., Duff, K., Irizarry, M.C., Stanley, H.E., Hyman, B.T., 2001. Plaque-induced abnormalities in neurite geometry in transgenic models of Alzheimer disease: implications for neural system disruption. J. Neuropathol. Exp. Neurol. 60, 753–758.
Lesne, S., Kotiline, K.L., Ashe, K.H., 2008. Plaque-bearing mice with reduced levels of oligomeric amyloid-beta assemblies have intact memory function. Neuroscience 151, 745–749.
Luchsinger, J.A., Tang, M.X., Siddiqui, M., Shea, S., Mayeux, R., 2004. Alcohol intake and risk of dementia. J. Am. Geriatr. Soc. 52, 540–546.
Lue, L.F., Kuo, Y.M., Roher, A.E., Brachova, L., Shen, Y., Sue, L., Beach, T., Kurth, J.H., RydEL, R.E., Rogers, J., 1999. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am. J. Pathol. 155, 853–862.
Makris, D., Kallithraka, S., Kefalas, P., 2006. Flavonols in grapes, grape products and wines: burden, profile and influential parameters. J. Food Compos. Anal. 19, 396–404.
MarianI, E., Polidori, M.C., Cherubini, A., Mecocci, P., 2005. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. J Chromatogr B Analyt Technol Biomed Life Sci 827, 65–75.
Masters, C.L., Multhaup, G., Simms, G., Pottgiesser, J., Martins, R.N., Beyreuther, K., 1985. Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. EMBO J. 4, 2757–2763.
Matcovitch-Natan, O., Winter, D.R., Giladi, A., Vargas Aguilar, S., Spinrad, A., Sarrazin, S., Ben-Yehuda, H., David, E., Zelada Gonzalez, F., Perrin, P., Keren-Shaul, H., Gury, M., Lara-Astaiso, D., Thaiss, C.A., Cohen, M., Bahar Halpern, K., Baruch, K., Deczkowska, A., Lorenzo-Vivas, E., Itzkovitz, S., Elinav, E., Sieweke, M. H., Schwartz, M., Amit, I., 2016. Microglia development follows a stepwise program to regulate brain homeostasis. Science 353, aad8670.
Mattivi, F., Guzzon, R., Vrhovsek, U., Stefanini, M., Velasco, R., 2006. Metabolite profiling of grape: flavonols and anthocyanins. J. Agric. Food Chem. 54, 7692–7702.
Mclean, C.A., Cherny, R.A., Fraser, F.W., Fuller, S.J., Smith, M.J., Beyreuther, K., Bush, A.I., Masters, C.L., 1999. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann. Neurol. 46, 860–866.
Mocanu, M.M., Nissen, A., Eckermann, K., Khlistunova, I., Biernat, J., Drexler, D., Petrova, O., Schonig, K., Bujard, H., Mandelkow, E., Zhou, L., Rune, G., Mandelkow, E.M., 2008. The potential for beta-structure in the repeat domain of tau protein determines aggregation, synaptic decay, neuronal loss, and coassembly with endogenous Tau in inducible mouse models of tauopathy. J. Neurosci. 28, 737–748.
Moreno, L., Puerta, E., Suarez-Santiago, J.E., Santos-Magalhaes, N.S., Ramirez, M.J., Irache, J.M., 2017. Effect of the oral administration of nanoencapsulated quercetin on a mouse model of Alzheimer's disease. Int. J. Pharm. 517, 50–57.
Morgan, D., 2005. Mechanisms of A beta plaque clearance following passive A beta immunization. Neurodegener. Dis. 2, 261–266.
Moussa, C., Hebron, M., Huang, X., Ahn, J., Rissman, R.A., Aisen, P.S., Turner, R.S., 2017. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J. Neuroinflammation 14, 1.
Mucke, L., Masliah, E., Yu, G.Q., Mallory, M., Rockenstein, E.M., Tatsuno, G., Hu, K., Kholodenko, D., Johnson-Wood, K., Mcconlogue, L., 2000. High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J. Neurosci. 20, 4050–4058.
Nasp, N.A.S.S.P., 2010. Alzheimer's Study Group, A National Alzheimer's Strategic Plan: the Report of the Alzheimer's Study Group. Alzheimer's Study Group, A National Alzheimer's Strategic Plan.
Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kayed, R., Metherate, R., Mattson, M.P., Akbari, Y., Laferla, F.M., 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39, 409–421.
Ono, K., Condron, M.M., Ho, L., Wang, J., Zhao, W., PasinettI, G.M., Teplow, D.B., 2008. Effects of grape seed-derived polyphenols on amyloid beta-protein self-assembly and cytotoxicity. J. Biol. Chem. 283, 32176–32187.
Orgogozo, J.M., Dartigues, J.F., Lafont, S., Letenneur, L., Commenges, D., Salamon, R., Renaud, S., Breteler, M.B., 1997. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Rev. Neurol. (Paris) 153, 185–192.

Paixao, J., Dinis, T.C., Almeida, L.M., 2012. Malvidin-3-glucoside protects endothelial cells up-regulating endothelial NO synthase and inhibiting peroxynitrite-induced NF-kB activation. Chem. Biol. Interact. 199, 192–200.
Palop, J.J., Chin, J., Mucke, L., 2006. A network dysfunction perspective on neurodegenerative diseases. Nature 443, 768–773.
Pasinetti, G.M., Wang, J., Ho, L., Zhao, W., Dubner, L., 2015. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. Biochim. Biophys. Acta 1852, 1202–1208.
Patel, N.S., Paris, D., Mathura, V., Quadros, A.N., Crawford, F.C., Mullan, M.J., 2005. Inflammatory cytokine levels correlate with amyloid load in transgenic mouse models of Alzheimer's disease. J. Neuroinflammation 2, 9.
Perry, V.H., Nicoll, J.A., Holmes, C., 2010. Microglia in neurodegenerative disease. Nat. Rev. Neurol. 6, 193–201.
Poulose, S.M., Thangthaeng, N., Miller, M.G., Shukitt-Hale, B., 2015. Effects of pterostilbene and resveratrol on brain and behavior. Neurochem. Int. 89, 227–233.
Pratheeshkumar, P., Son, Y.O., Wang, X., Divya, S.P., Joseph, B., Hitron, J.A., Wang, L., Kim, D., Yin, Y., Roy, R.V., Lu, J., Zhang, Z., Wang, Y., Shi, X., 2014. Cyanidin-3-glucoside inhibits UVB-induced oxidative damage and inflammation by regulating MAP kinase and NF-kappaB signaling pathways in SKH-1 hairless mice skin. Toxicol. Appl. Pharmacol. 280, 127–137.
Prince, M., 2015. World Alzheimer Report 2015: the Global Impact of Dementia: an Analysis of Prevalence, Incidence, Cost and Trends. INTERNATIONAL, A. S. D. https://www.alz.co.uk/research/world-report-2015.
Priprem, A., Watanatorn, J., Sutthiparinyanont, S., Phachonpai, W., Muchimapura, S., 2008. Anxiety and cognitive effects of quercetin liposomes in rats. Nanomedicine 4, 70–78.
Rice-Evans, C.A., Miller, N.J., Bolwell, P.G., Bramley, P.M., Pridham, J.B., 1995. The relative antioxidant activities of plant-derived polyphenolic flavonoids. Free Radic. Res. 22, 375–383.
Ries, M., Sastre, M., 2016. Mechanisms of abeta clearance and degradation by glial cells. Front. Aging Neurosci. 8, 160.
Rivero-Perez, M.D., Muniz, P., Gonzalez-Sanjose, M.L., 2008. Contribution of anthocyanin fraction to the antioxidant properties of wine. Food Chem. Toxicol. 46, 2815–2822.
Robinson, D.M., Keating, G.M., 2006. Memantine: a review of its use in Alzheimer's disease. Drugs 66, 1515–1534.
Rocher, A.B., Kinson, M.S., Luebke, J.I., 2008. Significant structural but not physiological changes in cortical neurons of 12-month-old Tg2576 mice. Neurobiol. Dis. 32, 309–318.
Ryan, J.M., Revilla, E., 2003. Anthocyanin composition of Cabernet Sauvignon and Tempranillo grapes at different stages of ripening. J. Agric. Food Chem. 51, 3372–3378.
Sabogal-Guaqueta, A.M., Munoz-Manco, J.I., Ramirez-Pineda, J.R., Lamprea-Rodriguez, M., Osorio, E., Cardona-Gomez, G.P., 2015. The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice. Neuropharmacology 93, 134–145.
Salganik, R.I., 2001. The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population. J. Am. Coll. Nutr. 20, 464S–472S discussion 473S-475S.
Santa-Maria, I., Diaz-Ruiz, C., Ksiezak-Reding, H., Chen, A., Ho, L., Wang, J., Pasinetti, G. M., 2012. GSPE interferes with tau aggregation in vivo: implication for treating tauopathy. Neurobiol. Aging 33, 2072–2081.
Scheff, S.W., Price, D.A., Schmitt, F.A., Dekosky, S.T., Mufson, E.J., 2007. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology 68, 1501–1508.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298, 789–791.
Selkoe, D.J., 2008. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav. Brain Res. 192, 106–113.
Sergides, C., Chirila, M., Silvestro, L., Pitta, D., Pittas, A., 2016. Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. Exp Ther Med 11, 164–170.
Serra, D., Paixao, J., Nunes, C., Dinis, T.C., Almeida, L.M., 2013. Cyanidin-3-glucoside suppresses cytokine-induced inflammatory response in human intestinal cells: comparison with 5-aminosalicylic acid. PloS One 8, e73001.
Shankar, G.M., Bloodgood, B.L., Townsend, M., Walsh, D.M., Selkoe, D.J., Sabatini, B.L., 2007. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J. Neurosci. 27, 2866–2875.
Shankar, G.M., Li, S., Mehta, T.H., Garcia-Munoz, A., Shepardson, N.E., Smith, I., Brett, F. M., Farrell, M.A., Rowan, M.J., Lemere, C.A., Regan, C.M., Walsh, D.M., Sabatini, B. L., Selkoe, D.J., 2008. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat. Med. 14, 837–842.
Sharma, V., Zhang, C., Pasinetti, G., Dixon, R., 2010. Fractionation of Grape Seed Proanthocyanidins for Bioactivity Assessment.
Siahmard, Z., Alaei, H., Reisi, P., Pilehvarian, A.A., 2012. The effect of red grape juice on Alzheimer's disease in rats. Adv. Biomed. Res. 1, 63.
Son, Y., Byun, S.J., Pae, H.O., 2013. Involvement of heme oxygenase-1 expression in neuroprotection by piceatannol, a natural analog and a metabolite of resveratrol, against glutamate-mediated oxidative injury in HT22 neuronal cells. Amino Acids 45, 393–401.
Spencer, J.P., 2009. The impact of flavonoids on memory: physiological and molecular considerations. Chem. Soc. Rev. 38, 1152–1161.
Spires, T.L., Meyer-Luehmann, M., Stern, E.A., Mclean, P.J., Skoch, J., Nguyen, P.T., Bacskai, B.J., Hyman, B.T., 2005. Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. J. Neurosci. 25, 7278–7287.
Stacchiotti, A., Favero, G., Rezzani, R., 2018. Resveratrol and SIRT1 Activators for the Treatment of Aging and Age-Related Diseases. Resveratrol - Adding Life to Years, Not Adding Years to Life. Intech Open.
Streit, W.J., Mrak, R.E., Griffin, W.S., 2004. Microglia and neuroinflammation: a pathological perspective. J. Neuroinflammation 1, 14.
Sugama, S., Takenouchi, T., Cho, B.P., Joh, T.H., Hashimoto, M., Kitani, H., 2009. Possible roles of microglial cells for neurotoxicity in clinical neurodegenerative diseases and experimental animal models. Inflamm. Allergy - Drug Targets 8, 277–284.
Tahara, K., Kim, H.D., Jin, J.J., Maxwell, J.A., Li, L., Fukuchi, K., 2006. Role of toll-like receptor signalling in Abeta uptake and clearance. Brain 129, 3006–3019.
Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., Deteresa, R., Hill, R., Hansen, L.A., Katzman, R., 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. 30, 572–580.
Theriault, P., Elali, A., Rivest, S., 2015. The dynamics of monocytes and microglia in Alzheimer's disease. Alzheimer's Res. Ther. 7, 41.
Truelsen, T., Thudium, D., Gronbaek, M., Copenhagen City Heart, S., 2002. Amount and type of alcohol and risk of dementia: the copenhagen city heart study. Neurology 59, 1313–1319.
Tsai, J., Grutzendler, J., Duff, K., Gan, W.B., 2004. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nat. Neurosci. 7, 1181–1183.
Tsuda, T., Shiga, K., Ohshima, K., Kawakishi, S., Osawa, T., 1996. Inhibition of lipid peroxidation and the active oxygen radical scavenging effect of anthocyanin pigments isolated from Phaseolus vulgaris L. Biochem. Pharmacol. 52, 1033–1039.
Tsuda, T., Horio, F., Osawa, T., 2000. The role of anthocyanins as an antioxidant under oxidative stress in rats. Biofactors 13, 133–139.
Udan, M.L., Ajit, D., Crouse, N.R., Nichols, M.R., 2008. Toll-like receptors 2 and 4 mediate Abeta(1-42) activation of the innate immune response in a human monocytic cell line. J. Neurochem. 104, 524–533.
Uddin, M.S., U, G.M.S., Begum, M.M., Begum, Y., Herrera-Calderon, O., Islam, M.M., Abdel-Daim, M.M., 2017. Inspection of phytochemical content and in vitro antioxidant profile of Gnaphalium luteoalbum L.: an unexplored phytomedicine. J. Pharm. Nutr. Sci. 7 (3), 136–146.
Urbanc, B., Cruz, L., Le, R., Sanders, J., Ashe, K.H., Duff, K., StanleY, H.E., Irizarry, M.C., Hyman, B.T., 2002. Neurotoxic effects of thioflavin S-positive amyloid deposits in transgenic mice and Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 99, 13990–13995.
Uttara, B., Singh, A.V., Zamboni, P., Mahajan, R.T., 2009. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr. Neuropharmacol. 7, 65–74.
Van Praag, H., Lucero, M.J., Yeo, G.W., Stecker, K., Heivand, N., Zhao, C., Yip, E., Afanador, M., Schroeter, H., Hammerstone, J., Gage, F.H., 2007. Plant-derived flavanol (-)epicatechin enhances angiogenesis and retention of spatial memory in mice. J. Neurosci. 27, 5869–5878.
Vingtdeux, V., Davies, P., Dickson, D.W., Marambaud, P., 2011. AMPK is abnormally activated in tangle- and pre-tangle-bearing neurons in Alzheimer's disease and other tauopathies. Acta Neuropathol. 121, 337–349.
Vitrac, X., Bornet, A., Vanderlinde, R., Valls, J., Richard, T., Delaunay, J.C., Merillon, J. M., Teissedre, P.L., 2005. Determination of stilbenes (delta-viniferin, trans-astringin, trans-piceid, cis- and trans-resveratrol, epsilon-viniferin) in Brazilian wines. J. Agric. Food Chem. 53, 5664–5669.
Walsh, D.M., Klyubin, I., Fadeeva, J.V., Cullen, W.K., Anwyl, R., Wolfe, M.S., Rowan, M. J., Selkoe, D.J., 2002. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416, 535–539.
Wang, H., Cao, G., Prior, R.L., 1997. Oxygen radical absorbing capacity of anthocyanins. J. Agric. Food Chem. 45, 304–309.
Wang, J., Dickson, D.W., Trojanowski, J.Q., Lee, V.M., 1999. The levels of soluble versus insoluble brain Abeta distinguish Alzheimer's disease from normal and pathologic aging. Exp. Neurol. 158, 328–337.
Wang, H.W., Pasternak, J.F., Kuo, H., Ristic, H., Lambert, M.P., Chromy, B., Viola, K.L., Klein, W.L., Stine, W.B., Krafft, G.A., Trommer, B.L., 2002. Soluble oligomers of beta amyloid (1-42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus. Brain Res. 924, 133–140.
Wang, J., Ho, L., Zhao, Z., Seror, I., HumalA, N., Dickstein, D.L., Thiyagarajan, M., Percival, S.S., Talcott, S.T., Pasinetti, G.M., 2006. Moderate consumption of Cabernet Sauvignon attenuates Abeta neuropathology in a mouse model of Alzheimer's disease. Faseb. J. 20, 2313–2320.
Wang, J., Ho, L., Zhao, W., Ono, K., Rosensweig, C., Chen, L., Humala, N., Teplow, D.B., Pasinetti, G.M., 2008. Grape-derived polyphenolics prevent Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J. Neurosci. 28, 6388–6392.
Wang, X., Su, B., Zheng, L., Perry, G., Smith, M.A., Zhu, X., 2009a. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J. Neurochem. 109 (Suppl. 1), 153–159.
Wang, Y.J., Thomas, P., Zhong, J.H., Bi, F.F., Kosaraju, S., Pollard, A., Fenech, M., Zhou, X.F., 2009b. Consumption of grape seed extract prevents amyloid-beta deposition and attenuates inflammation in brain of an Alzheimer's disease mouse. Neurotox. Res. 15, 3–14.
Wang, J., Santa-Maria, I., Ho, L., Ksiezak-Reding, H., Ono, K., Teplow, D.B., Pasinetti, G. M., 2010. Grape derived polyphenols attenuate tau neuropathology in a mouse model of Alzheimer's disease. J Alzheimers Dis 22, 653–661.

Wang, J., Ferruzzi, M.G., Ho, L., Blount, J., Janle, E.M., Gong, B., Pan, Y., Gowda, G.A., Raftery, D., Arrieta-Cruz, I., Sharma, V., Cooper, B., Lobo, J., Simon, J.E., Zhang, C., Cheng, A., Qian, X., Ono, K., Teplow, D.B., Pavlides, C., Dixon, R.A., Pasinetti, G.M., 2012. Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment. J. Neurosci. 32, 5144–5150.

Wang, J., Tang, C., Ferruzzi, M.G., Gong, B., Song, B.J., Janle, E.M., Chen, T.Y., Cooper, B., Varghese, M., Cheng, A., Freire, D., Bilski, A., Roman, J., Nguyen, T., Ho, L., Talcott, S.T., Simon, J.E., Wu, Q., Pasinetti, G.M., 2013. Role of standardized grape polyphenol preparation as a novel treatment to improve synaptic plasticity through attenuation of features of metabolic syndrome in a mouse model. Mol. Nutr. Food Res. 57, 2091–2102.

Wang, J., Bi, W., Cheng, A., Freire, D., Vempati, P., Zhao, W., Gong, B., Janle, E.M., Chen, T.Y., Ferruzzi, M.G., Schmeidler, J., Ho, L., Pasinetti, G.M., 2014. Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease-experimental approach and therapeutic implications. Front. Aging Neurosci. 6, 42.

Wang, D., Ho, L., Faith, J., Ono, K., Janle, E.M., Lachcik, P.J., Cooper, B.R., Jannasch, A. H., D'arcy, B.R., Williams, B.A., Ferruzzi, M.G., Levine, S., Zhao, W., Dubner, L., Pasinetti, G.M., 2015. Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease beta-amyloid oligomerization. Mol. Nutr. Food Res. 59, 1025–1040.

Weiner, H.L., Frenkel, D., 2006. Immunology and immunotherapy of Alzheimer's disease. Nat. Rev. Immunol. 6, 404–416.

Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W., 1975. A protein factor essential for microtubule assembly. Proc. Natl. Acad. Sci. U. S. A. 72, 1858–1862.

Wilcock, D.M., Griffin, W.S., 2013. Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. J. Neuroinflammation 10, 84.

Wilkinson, K., El Khoury, J., 2012. Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int. J. Alzheimer's Dis. 2012, 489456.

Wyss-Coray, T., 2006. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat. Med. 12, 1005–1015.

Xu, Y., Simon, J.E., Welch, C., Wightman, J.D., Ferruzzi, M.G., Ho, L., Pasinetti, G.M., Wu, Q., 2011. Survey of polyphenol constituents in grapes and grape-derived products. J. Agric. Food Chem. 59, 10586–10593.

Yankner, B.A., Duffy, L.K., Kirschner, D.A., 1990. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides. Science 250, 279–282.

Yu, K.C., Kwan, P., Cheung, S.K.K., Ho, A., Baum, L., 2018. Effects of resveratrol and morin on insoluble tau in tau transgenic mice. Transl. Neurosci. 9, 54–60.

Zaplatic, E., Bule, M., Shah, S.Z.A., Uddin, M.S., Niaz, K., 2019. Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease. Life Sci. 224, 109–119.

Zhao, H., Wang, Q., Cheng, X., Li, X., Li, N., Liu, T., Li, J., Yang, Q., Dong, R., Zhang, Y., Zhang, L., 2018. Inhibitive effect of resveratrol on the inflammation in cultured astrocytes and microglia induced by abeta1-42. Neuroscience 379, 390–404.

Zhu, X., Smith, M.A., Perry, G., Aliev, G., 2004. Mitochondrial failures in Alzheimer's disease. Am J Alzheimers Dis Other Demen 19, 345–352.