Joana Angélica de Sousa Loureiro

The relevance of natural compounds in the Alzheimer´s Disease

Faculdade Ciências da Saúde

Universidade Fernando Pessoa

Porto, 2018

Joana Angélica de Sousa Loureiro

The relevance of natural compounds in the Alzheimer´s Disease

Faculdade Ciências da Saúde

Universidade Fernando Pessoa

Porto, 2018

The relevance of natural compounds in the Alzheimer´s Disease

---

Joana Angélica de Sousa Loureiro

(assinatura)

Trabalho apresentado à Universidade Fernando Pessoa como parte dos requisitos para obtenção de grau de Mestre em Ciências Farmacêuticas.

Sumário

A incidência da doença de Alzheimer (DA), uma doença neurodegenerativa, é promovida pelo aumento da idade. Esta doença afeta a memória e outras funções cognitivas com intensidade suficiente para produzir uma perda funcional. É a causa mais comum de demência em idosos. O aumento contínuo da incidência da DA exige o desenvolvimento urgente de uma terapêutica. Embora os estudos sobre essa doença estejam a avançar rapidamente, até o momento, poucos medicamentos para retardar a progressão da doença estão disponíveis no mercado. Nas últimas décadas, vários compostos com diversas atividades farmacológicas extraídas de frutas, vegetais e ervas demonstraram ter uma potencial eficácia contra a DA por meio de múltiplas alterações patológicas da doença. A diversidade de compostos bioativos presentes nesses produtos naturais desempenha um papel crucial na prevenção e no tratamento da DA.

Palavras-chave:

Doença de Alzheimer, Doenças neurodegenerativas, Compostos naturais

Abstract

The incidence of Alzheimer's disease (AD), a neurodegenerative disease, is promoted by the increase of the age. This disease affects the memory and other cognitive functions with sufficient intensity to produce a functional loss, and it is the most common cause of dementia in the elderly. The continuous increase in the incidence of AD demands the urgent development of new therapies. Although, studies on this disease are advancing quickly, until the moment just few drugs to delay the progression of the disease are available for the patients. In recent decades, a number of compounds with diverse pharmacological activities extracted from fruits, vegetables and herbs demonstrated to have potential efficacies against AD via targeting multiple pathological changes of this disease. The diverse array of bioactive compounds presented in these natural products plays a crucial role in prevention and treatment of AD.

Key words

Alzheimer´s disease, Neurodegenerative diseases, Natural compounds

Index

Table Index

Abbreviations

Aβ - Amyloid beta peptide

APP - Amyloid precursor protein

BBB – Blood-brain barrier

COX - Cyclo-oxygenase

DA – Doença de Alzheimer´s

DHA - Docosahexanoic acid

DNA - Deoxyribonucleic acid

EGCG - Epigallocatechin gallate

NFTs - Neurofibrillary tangles

NSAIDs - Non-steroidal anti-inflammatory drugs

PS - Presenilin protein

RNS - Reactive nitrogen species

ROS - Reactive oxygen species

I. Introduction

The increase of the age promotes the incidence of neurodegenerative diseases. These diseases destabilize significantly the memory and other cognitive functions with sufficient intensity to produce a functional loss, such as carrying out everyday activities or recognizing people and places (Brookmeyer, Johnson *et al.* 2007).

Alzheimer's disease (AD) is known as the most important neurodegenerative disease and the most common cause of dementia among the elderly, counting with around 70% of dementia cases worldwide (Alzheimer, Stelzmann *et al.* 1995, LaFerla and Oddo 2005, Castellani, Rolston *et al.* 2010, Kumar, Singh *et al.* 2015).

Based on empirical observations, natural compounds were the first medicines available, and were used for a long time (Lahlou 2007, Ganesan 2008). The study of novel drug candidates has revealed that natural products have a giant potential to become drug leads with neuroprotective activity. Given that the creation of big quantities of compounds isolated from natural products is extremely protracted and expensive, there is a great interest for the mixtures of compounds obtained from extracts of plant material or from microbial broths (Harvey 2008).

A diversity of natural compounds has been reported to be effective for the prevention and cure of AD. The potential of natural products for the inhibition of amyloid peptides aggregation *in vitro* and for the delay of progression of the disease in animal models is supported by various experimental studies. Several fruits, plants, animals, marine organisms or microorganisms have important bioactive compounds essential for the prevention and cure of various diseases without undesirable side effects, including AD.

In this review, a detailed description of natural compounds with beneficial effects in AD and their mechanisms of action is reported and sorted by order by alphabet order. The use of natural compounds is a promising approach for AD therapy.

II. Relevant approaches to treat Alzheimer´s Disease

Nowadays none medications appears to be able to cure AD or to stop the progression of disease (Clark and Karlawish 2003, Scarpini, Scheltens *et al.* 2003, Cummings 2004, Barage and Sonawane 2015).

So, there is a tremendous medical need for the development of novel therapeutic strategies that target the underlying pathogenic mechanisms in AD. It is obvious from the literature that amyloid beta peptide (Aβ) plays the main role in the pathogenesis of AD. Therefore, according to the amyloid cascade hypothesis novel therapeutic strategies that inhibit Aβ production/aggregation or to increase Aβ clearance from the brain or prevent the formation of the presumed neurotoxic oligomeric Aβ species are predicted to stop or retard the progression of neurodegeneration and dementia in AD (Blennow, de Leon *et al*. 2006, Klafki, Staufenbiel *et al.* 2006). Others strategies to treat AD are being developed such as tau based therapeutics, the use of anti-inflammatory drugs and the use of antioxidants.

Secretase modulators: The most direct approach in anti-amyloid therapy is the decrease of $A\beta_{1-42}$ production. Aβ derives from the proteolytic cleavage of amyloid precursor protein (APP), by the sequential action of two proteases: β- and γ-secretases (amyloidogenic pathway). A third protease, α-secretase, which competes with β-secretase for the APP substrate, can preclude the Aβ production by cleaving the peptide in two (non-amyloidogenic pathway). Thus, this scenario suggests three strategies to reduce Aβ that have been intensely studied for more than a decade: the inhibition of β and γ-secretases or the stimulation of α-secretase (Verdile, Fuller *et al.* 2004, Citron 2010).

Despite the development in production of γ-secretase inhibitors, there are many issues related with their potential effects on Notch signaling, effects on known or unidentified γ-secretase substrates, and the effects of the accumulation of potentially neurotoxic APP C-terminal fragments as a result of inhibiting γ-secretase (Hadland, Manley *et al*. 2001). For these reasons, it is believed that β-secretase is a better therapeutic target because do not produce Aβ and do not have clear pathological phenotypes (Luo, Bolon *et al*. 2001). Therefore, β-secretase is a major therapeutic target for the development of inhibitor

drugs to reduce brain Aβ concentrations (Ballard, Gauthier *et al*. 2011, Barage and Sonawane 2015). Regarding α-secretase, this protease cleaves APP in the transmembrane region, within the Aβ domain of the APP releasing soluble APP which has neuroprotective effects and improves the memory (Barage and Sonawane 2015). Thus, drugs that stimulate the activity of α-secretase can change APP processing towards the non-amyloidogenic pathway impeding the Aβ formation which is considered a therapeutic approach for AD (Blennow, de Leon *et al.* 2006, Fahrenholz 2007).

Inhibition of Aβ aggregation or fibrillation: The proteolytic cleavage of APP, by the sequential action of β- and γ-secretases releases Aβ peptide monomers that initially have α-helix conformation followed by extensive conformational transitions from α-helix to β-sheet. Aβ monomers, in particular $A\beta_{1-42}$, rapidly form self-aggregates to produce oligomers aggregates that are thought to initiate the pathogenic cascade. Then, oligomers aggregate in protofibrils, fibrils and finally develop the Aβ plaques (Kirkitadze, Condron *et al*. 2001, Xu, Shen *et al.* 2005, Walsh and Selkoe 2007, Ahmed, Davis *et al*. 2010). Initially, it was assumed that only Aβ that had aggregated into the fibrils that constitute the Aβ plaques would exert toxic effects. However, in recent years studies have suggested that the formation of oligomers rather than insoluble amyloid plaques may play an essential role in the AD neurodegenerative cascade (Arendt 2009). It is believed that Aβ oligomers can be more toxic than mature fibrils by inducing synaptic dysfunction (Walsh and Selkoe 2007, Shankar, Li *et al.* 2008, Ballard, Gauthier *et al*. 2011). Promising approaches for the development of small-molecule drugs that interact with the Aβ, blocking the interactions Aβ–Aβ represents another attractive approach. These molecules prevent the formation of toxic Aβ oligomers. That way, this molecules that could prevent or treat AD (Klafki, Staufenbiel *et al*. 2006).

Aβ degradation and clearance: The imbalance between production and clearance of the Aβ peptide is responsible for pathological events in AD (Kurz and Perneczky 2011). The augmented level of Aβ peptides within the brain is caused by the excess of production or by deficient clearance of Aβ peptide (Bates, Verdile *et al.* 2009). Several causes can reduce the clearance of Aβ peptide such as increased aggregation, imperfect

degradation, troubled transport across the blood-brain barrier (BBB) or inefficient peripheral removal of the peptide (Mawuenyega, Sigurdson *et al.* 2010, Sagare, Bell *et al*. 2012). That way over the past several years these mechanisms have been targeted for several studies (Tanzi, Moir *et al*. 2004, Kurz and Perneczky 2011).

Immunotherapy: In the last years, Aβ immunotherapy has become one of the most promising areas in research of AD, through either active Aβ peptide vaccination or passive infusion of anti-Aβ monoclonal antibodies (Solomon, Koppel *et al.* 1997, Schenk, Barbour *et al.* 1999, Bard, Cannon *et al.* 2000). The immunotherapy seems to be one promising approach for preventing and treating AD. It is believed that the use of antibodies against Aβ peptide clears Aβ deposits (Alves, Correia *et al*. 2012).

In the first study, the importance of immunotherapy through the active immunization in AD transgenic mice was studied and the results demonstrated an attenuated deposition of Aβ and neutralization of Aβ oligomers, blocking the toxic effects of Aβ on cells (Solomon, Koppel *et al.* 1997, Schenk, Barbour *et al*. 1999, Hartman, Izumi *et al*. 2005, Klyubin, Walsh *et al*. 2005). The authors proposed that Aβ immunization stimulates a highly specific immune response to clear Aβ, reducing the pathology in the animal model (Schenk, Barbour *et al*. 1999). Sustaining this hypothesis, antibodies can block and even reverse Aβ aggregation and toxicity *in vitro* (Solomon, Koppel *et al*. 1997, Frenkel, Katz *et al.* 2000, Du, Wei *et al.* 2003). Additionally, Aβ immunization shown the decrease a variety of aspects of the amyloid associated pathology including neuritic dystrophy, synaptic degeneration and tau accumulation (Lombardo, Stern *et al*. 2003, Oddo, Billings *et al.* 2004, Brendza, Bacskai *et al*. 2005, Buttini, Masliah *et al.* 2005). Comparable results were obtained using passive immunisation with antibodies against Aβ (Bard, Cannon *et al.* 2000).

There is some skepticism about how this approach works, because only a small quantity of antibody crosses the BBB. Four models of antibody-mediated amyloid clearance were proposed. The first model - microglia mediated - suggests that a small amount of amyloid-specific antibodies reaches amyloid deposits in the brain, triggering a phagocytic response by microglia. In the second model - direct resolution - amyloid-specific antibodies interact with amyloid deposits in the brain. The third model -

peripheral sink - suggests that amyloid-specific antibodies act as a peripheral sink for soluble Aβ species, leading ultimately to the resolution of brain deposits by pulling soluble Aβ into the periphery, where it is quickly cleared. In the fourth and last model - blockade of toxic oligomers - amyloid-specific antibodies rapidly bind to Aβ oligomers, inhibiting their toxic effects without immediate effect on amyloid load (Citron 2010).

Inhibition of tau aggregation or tau hyperphosphorylation: Tau, a microtubule-associated protein responsible for the assembly and stability of microtubules in the neuronal cell and for axoplasmatic transport, is the major constituent of neurofibrillary tangles (NFTs). These characteristic structures observed in AD neurons are constituted by tau hyperphosphorylated (Lee, Goedert *et al.* 2001, Gotz, Schild *et al*. 2004, Goedert, Klug *et al.* 2006, Small and Duff 2008, Herrup 2010, Alves, Correia *et al*. 2012). Tau is a soluble protein, but insoluble aggregates are produced during the formation of NFTs, which disrupt the structure and function of the neuron. Initially, tau monomers bind and form oligomers, which then aggregate into a β-sheet before form the NFTs (Hardy and Selkoe 2002, Meraz-Ríos, León *et al*. 2010, Ballard, Gauthier *et al*. 2011). Studies with human AD patients proved that the severity of dementia is strongly connected with NFTs density *(Wilcock and Esiri 1982, Arriagada, Growdon et al.* 1992, Nagy, Jobst *et al.* 1996).

Thus, substances that can inhibit tau aggregation or the blockade of tau hyperphosphorylation can to be a potential treatment strategy, protecting the neurons from neurofibrillary degeneration (Chirita, Necula *et al.* 2004, Pickhardt, Gazova *et al.* 2005, Lee and Trojanowski 2006, Schneider and Mandelkow 2008).

Anti-inflammatory drugs: Induction of inflammatory responses is known to play an essential role in the progression of AD, and it is proposed as a mechanism by which Aβ could modulate its toxic effects. The insoluble Aβ peptides deposits and NFTs provide evident stimuli for inflammation (Wenk 2003). Several studies showed that Aβ stimulates macrophages and microglia and induces the release of cytokines. Thus, anti-inflammatory drugs may be beneficial in slowing the rate of neurodegeneration in AD (Clippingdale, Wade *et al.* 2001). The anti-inflammatory drugs can be an attractive target therapeutic option because the targeting inflammatory cascade in AD could

decrease damaging effects and stimulate clearance of abnormal protein (Schott and Revesz 2013).

A large amount of epidemiological studies proposes that the risk of the AD in patients is reduced when treated with non-steroidal anti-inflammatory drugs (NSAIDs) (Aisen 2002). Evidence from multiple studies showed that risk reduction occurs in AD of approximately 50% when the use of NSAIDs is made a long-term (Wyss-Coray 2006). High concentrations of numerous NSAIDs show the decrease of $A\beta_{1-42}$ in AD transgenic mice without affecting Notch cleavage, while simultaneously the production of smaller Aβ isoforms that are expected to be less prone to aggregation than $A\beta_{1-42}$ increase (Weggen, Eriksen *et al.* 2001). This reduction in Aβ levels may be caused by either inhibition of cyclo-oxygenase (COX) or by a direct effect on γ-secretase (Weggen, Eriksen *et al*. 2001, Eriksen, Sagi *et al*. 2003). One *in vitro* study has revealed that NSAIDs do not modify the total levels of Aβ produced but rather shift cleavage from $A\beta_{1-42}$ to a shorter 38 amino acid form ($A\beta_{1-38}$), suggesting that the activity of γ-secretase cleavage is altered in response to NSAIDs. Despite the role of $A\beta_{1-38}$ in AD pathogenesis to be unknown yet, it is well accepted that the longer Aβ is more amyloidogenic, such as the case of $A\beta_{1-42}$. Thus, this therapeutic approach warrants further investigation (Weggen, Eriksen *et al.* 2001).

Antioxidants: The intensification of oxidative stress related with AD can play a significant role in the neurodegeneration of neurons. Thus, antioxidants have been proposed as potential therapeutics (Clippingdale, Wade *et al*. 2001).

III. Natural compounds and their effects on Alzheimer´s Disease

A natural product is defined as being a chemical compound or substance that is produced by natural sources found in nature including plants, animals, marine organisms or microorganisms, that typically has a pharmacological or biological properties useful in pharmaceutical drug discovery.

Natural product and natural extracts were the first medicines applied in the empirical treatment of different type of diseases. The discovering of new therapeutic molecules demonstrates that natural products have a huge potential in the treatment of an enormous variety of pathologies.

The most studied compounds were presented below and listed in table 1.

Apigenin: Apigenin (4',5,7-tetrahydroxyflavone) is a flavonoid and a pharmacologically active agent that can be isolated from several plants, herbs, fruits and vegetables. Apigenin is particularly abundant in the ligulate flowers of the chamomile plant (around 68% of total flavonoids is apigenin) and found in smaller concentrations in other sources such as cabbage, celery, parsley and bell pepper (McKay and Blumberg 2006, Shukla and Gupta 2010). Several studies have demonstrated that apigenin exhibits a diversity of biological effects, including anti-inflammatory and antioxidant (Panes, Gerritsen *et al.* 1996, Gupta, Afaq *et al*. 2001, Jin, Qian *et al*. 2009, Balez, Steiner *et al.* 2016). Apigenin has been the subject of interests in recent years as a beneficial and health promoting agent due to the several biological effects and its low intrinsic toxicity (Choi, Islam *et al.* 2014). One study with apigenin showed that this compound can affect APP processing through the inhibition of β-secretase thereby preventing Aβ deposition and decrease the insoluble Aβ levels (Zhao, Wang *et al.* 2013). It is a potent chelating agent that reduces the metal ions participating in radical reactions and therefore reduces the creation of free radicals. Furthermore, apigenin could serve as an antioxidant to eliminate free radicals such as oxygen, nitric oxide, and superoxide anion (Sugihara, Arakawa *et al*. 1999). Evidences have showed that apigenin protects rat cortical neurons against Aβ-induced neurotoxicity (Butterfield, Reed *et al*. 2007).

Asiatic acid: Asiatic acid is a pentacyclic triterpene isolated from a variety of plants, including *Centella asiatica*. A study with asiatic acid showed that this compound significantly affects APP processing through the inhibition of β-secretase and the increase of α-secretase (non-amyloidogenic pathway). The direct inhibition of β-secretase is known to increase non-amyloidogenic processing. In addition, the study suggests that the asiatic acid is able to activate Aβ clearance mechanisms (Patil, Maki *et al.* 2010). A significant decrease in Aβ was detectable in PSAPP mice (Dhanasekaran, Holcomb *et al.* 2009). A recent study affirmed that the extract of asiatic acid attenuated Aβ-associated behavioral abnormalities in the Tg2576 mouse, a murine model of AD. *In vitro*, this natural compound protected SH-SY5Y cells and MC65 human neuroblastoma cells from toxicity induced by exogenously added and endogenously generated Aβ, respectively (Soumyanath, Zhong *et al.* 2012). Asiatic acid improves learning and memory *in vivo*, with several studies suggesting that antioxidant mechanisms explain cognitive benefits (Gupta, Veerendra Kumar *et al.* 2003, Gnanapragasam, Ebenezar *et al.* 2004). Asiatic acid reduces brain oxidative stress including in AD animal models (male Wistar rats), scavenges free radicals, reduces lipid peroxidation and protects against deoxyribonucleic acid (DNA) damage (Gupta, Veerendra Kumar *et al*. 2003, Veerendra Kumar and Gupta 2003, Shinomol and Muralidhara 2008, Dhanasekaran, Holcomb *et al*. 2009).

Baicalein: Baicalein is a flavonoid extracted from the roots of chinese herbal medicine *Scutellaria baicalensis (Heo, Kim et al. 2004, Lu, Ardah et al. 2011, Zhang, Obregon et al*. 2013). Some studies show the importance of this compound in AD. Studies have suggested that baicalein can reduce the cytotoxicity of Aβ, probably by a decrease of oxidative stress, through inhibition of reactive oxygen species production (Heo, Kim et al. 2004, Choi, Choi *et al*. 2010, Moslehi, Meshkini *et al*. 2012, Bend, Xia *et al*. 2015). Baicalein inhibited Aβ-induced membrane damage and neurotoxicity in a dose dependent pattern (Heo, Kim *et al*. 2004). The effect of baicalein on Aβ aggregation and toxicity was also studied. The results proved that baicalein could inhibit Aβ fibrillation and oligomerisation, disaggregate pre-formed Aβ amyloid fibrils and prevent Aβ fibril-induced toxicity (Lu, Ardah *et al*. 2011). Existing Aβ fibrils are disaggregated by baicalein, suggesting that the depolymerization of Aβ fibrils happened (Song, Wang et

al. 2012). A study also suggests that baicalein promotes a non-amyloidogenic pathway of APP processing, by the increase of α-secretase and the reduction of β-secretase activity. Thereby, it reduces the Aβ production. Also, it was observed that baicalein is able to prevent phosphorylation of tau in APP/PS1 mice and improve cognitive performance (Zhang, Obregon *et al.* 2013, Wei, Tang *et al*. 2014, Gu, Xu *et al*. 2016).

Berberine: Berberine is a natural isoquinoline alkaloid isolated from *Rhizoma coptidis*, an important herb widely used in Chinese herbal medicine (Asai, Iwata *et al*. 2007, Ji and Shen 2011). Some studies have been conducted to verify its importance in AD. Evidences suggest that berberine reduces extracellular Aβ levels by the alteration in APP processing (Asai, Iwata *et al*. 2007, Durairajan, Liu *et al*. 2012). More specifically, berberine reduce the Aβ production by inhibition of β-secretase expression in a rabbit model of AD (male New Zealand white rabbits) (Zhu, Wu *et al.* 2011, Zhu, Wu *et al*. 2011, Panahi, Mahmoudian *et al.* 2013, Huang, Jiang *et al.* 2017). The treatment of TgCRND8 mice, a well-established transgenic mouse model of AD, with berberine also inhibited significantly the hyperphosphorylation of APP and tau (Yu, Tian *et al*. 2011, Durairajan, Liu *et al.* 2012). Also, berberine has been also demonstrates to be advantageous to AD through their anti-inflammation properties, antioxidative effects scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS) and suppressing lipid peroxidation involved in Aβ formation and accumulation (Rackova, Majekova *et al*. 2004, Yokozawa, Ishida *et al*. 2004, Asai, Iwata *et al*. 2007, Xu and Zhou 2010, Yu, Tian *et al.* 2011, Jia, Liu *et al*. 2012, Abd El-Wahab, Ghareeb *et al*. 2013, Xu, Zhang *et al*. 2013, Das, Mazumder *et al*. 2015). A recent work finds that berberine could promote Aβ clearance and inhibit Aβ production in the triple-transgenic mouse model of AD (3×Tg-AD). A reduction of extracellular and intracellular Aβ, APP levels and Aβ plaque deposition in the hippocampus of AD mice was observed (Huang, Jiang *et al*. 2017).

Caffeine: Caffeine is a methylxanthine and probably the most widely consumed psychoactive substance in the world. The principal source of caffeine is the coffee bean, from which coffee is brewed (Arendash, Schleif *et al.* 2006). Caffeine is present in numerous dietary sources consumed around the world, including coffee, tea, cocoa beverages, candy bars, and soft drinks (Nehlig 1999). Epidemiological studies have

shown that caffeine consumption has an inverse relation with the incidence of AD (Maia and de Mendonca 2002). The long-term ingestion of caffeine is directly related with improved cognitive performance and memory. This benefic effect may be due to reduced expression of presenilin (PS)1, β-secretase and γ-secretase, indicating that decreased Aβ production can be a mechanism of caffeine cognitive protection (Arendash, Schleif *et al.* 2006, Arendash, Mori *et al*. 2009). An epidemiological study suggested that caffeine consumption resulted in lower cortical and hippocampal Aβ level, including $A\beta_{1–40}$ and $A\beta_{1–42}$ (Arendash, Schleif *et al.* 2006, Arendash, Mori *et al*. 2009, Cao, Cirrito *et al.* 2009, Chu, Chang *et al*. 2012, Soliman, Geiger *et al*. 2017). The caffeine administration significantly reduced the $A\beta_{1–42}$ levels in cortex and hippocampus, 51 and 59%, respectively, when compared to controls. Similarly, $A\beta_{1–40}$ levels reduced 25% in cortex and 37% in hippocampus after the caffeine treatment (Arendash, Mori *et al*. 2009). The reduction of Aβ levels can be due to the ability of caffeine to inhibit the formation of β-sheets (Sharma, Kalita *et al.* 2016). Caffeine has been suggested as anti-inflammatory and antioxidant compound (Brothers, Marchalant *et al.* 2010, Prasanthi, Dasari *et al*. 2010, Prasanthi, Dasari *et al*. 2010, Ruiz-Medina, Pinto-Xavier *et al*. 2013, Ullah, Ali *et al*. 2015). In addition to the processes mentioned above, caffeine can protect against AD pathology through its antioxidant properties. The reduction in Aβ levels after the administration caffeine can be associated with reduction in oxidative stress (Prasanthi, Dasari *et al*. 2010). The improved memory caused by caffeine can be also associated with reduced hippocampal tau phosphorylation and proteolytic fragments (Prasanthi, Dasari *et al.* 2010, Prasanthi, Dasari *et al.* 2010, Currais, Kato *et al.* 2011, Laurent, Eddarkaoui *et al.* 2014). Besides, a study demonstrated that caffeine can enhance brain Aβ clearance, and this effect could explain, in part, the protective effect of caffeine against AD (Qosa, Abuznait *et al*. 2012).

Colostrinin: Colostrinin is a mixture of proline-rich polypeptides derived from colostrums. This is a form of milk produced by mammary glands in the final step of the pregnancy (Popik, Bobula *et al.* 1999). *In vitro* evidences have revealed that colostrinin inhibits Aβ aggregation and the formation of short Aβ fibrils. Also, it simplifies the disassembly of existing aggregates by disrupting β-sheet bonding (Popik, Bobula *et al.* 1999, Schuster, Rajendran *et al*. 2005). Additionally, a study demonstrates that

colostrinin can solubilize Aβ fibrils reducing de fibril formation (Bourhim, Kruzel *et al.* 2007). Colostrinin facilitated spatial learning and helped to maintain cognitive and daily functions in patients with mild to moderate AD (Popik, Bobula *et al.* 1999, Schuster, Rajendran *et al.* 2005). In addition, a study showed that colostrinin alters gene expression of molecular networks concerned in APP synthesis, tau phosphorylation and increased levels of enzymes that proteolitically eliminate Aβ (Szaniszlo, German *et al.* 2009). Moreover, studies have revealed that colostrinin is an oxidative stress modulator and decreased the expression of inflammatory chemokines and cytokines (Boldogh and Kruzel 2008, Szaniszlo, German *et al*. 2009). Studies on cultured cells demonstrated that colostrinin modulates intracellular levels of ROS, via regulation of glutathione metabolism, activity of antioxidant enzymes and mitochondria function (Boldogh and Kruzel 2008).

Crocin: Crocin is the main carotenoid present in the saffron flower (*Crocus sativus*) stigma and it has many medicinal properties. An experiment showed that crocin inhibited the fibril formation due to their ability to bind to the Aβ hydrophobic regions (Papandreou, Kanakis *et al.* 2006). Crocin decreased the number of fibrils formed and significantly reduced the average fibril length of $A\beta_{1\text{-}40}$ (Ghahghaei, Bathaie *et al*. 2012). An additional study affirmed that the anti-amyloidogenic effect of crocin may be exerted not only by the inhibition of Aβ fibril formation but also by the disruption of Aβ aggregates (Ghahghaei, Bathaie *et al.* 2013). Besides, other studies affirmed that the beneficial effects of crocin on memory processing might be attributed to its favorable antioxidant and anti-inflammatory effects (Nam, Park *et al*. 2010, Naghizadeh, Mansouri *et a*l. 2013, Finley and Gao 2017).

Curcumin: Curcumin, or diferuloylmethane, is a well-known active ingredient used in the traditional herbal remedy and Indian cuisine. It is isolated from the root of *Curcuma longa* L. (Ak and Gulcin 2008). Curcumin may represent a promising approach for preventing or treating AD because it has a number of beneficial properties with neuroprotective efficacy, including anti-inflammatory, antioxidant, and anti-fibrilogenic activities. *In vivo* and *in vitro* studies demonstrated the ability of curcumin to inhibit the generation of Aβ, formation of Aβ oligomers, Aβ fibrils, formation of amyloid plaques, and Aβ aggregation, but also destabilizing preformed Aβ fibrils (Ono, Hasegawa *et al*.

2004, Yang, Lim *et al.* 2005, Zhang, Si *et al*. 2010, Zhang, Zhang *et al*. 2011, Caesar, Jonson *et al*. 2012, Huang, Chang *et al.* 2012, Zhang, Sun *et al*. 2013, Wang, Su *et al*. 2014, Wang, Xu *et al.* 2015, Thapa, Jett *et al.* 2016). Besides that, curcumin reduced Aβ deposition improving cognitive performance in a transgenic animal model of AD (5XFAD) (McClure, Ong *et al*. 2017). Curcumin treatment was found to decrease Aβ production by attenuating the maturation of APP in the secretory pathway *(*Lim, Chu *et al*. 2001, Zhang, Browne *et al.* 2010). In addition, it was reported that curcumin suppressed the up-regulation of APP, β and γ-secretase levels and also decreased PS1 (Lin, Chen *et al*. 2008, Shimmyo, Kihara *et al*. 2008, Zhang, Browne *et al*. 2010, Zhang, Si *et al*. 2010, Xiong, Hongmei *et al*. 2011, Zhang, Zhang *et al*. 2011, Zhang, Sun *et al*. 2013, Wang, Su *et al.* 2014). A recent research showed that curcumin administration dramatically reduced Aβ production by downregulating β-secretase, preventing synaptic degradation, and improving spatial learning and memory impairment of 5×FAD mice (Zheng, Dai *et al*. 2017). On the other hand, curcumin decrease tau hyperphosphorylation (Park, Kim *et al*. 2008, Lin, Yu *et al.* 2013). Several other beneficial effects have been attributed to curcumin, including anti-inflammatory and antioxidant properties (Lim, Chu *et al.* 2001, Aggarwal, Kumar *et al*. 2003, Shimmyo, Kihara *et al*. 2008, Ray and Lahiri 2009, Huang, Chang *et al.* 2012, Shi, Zheng *et al.* 2015, Yang, Liang *et al*. 2015, Huang, Zheng *et al*. 2016, Uğuz, Öz *et al.* 2016).

Docosahexaenoic acid: Docosahexanoic acid (DHA) is an essential n-3 polyunsaturated fatty acid found predominantly in marine fish and algae. This polyunsaturated fatty acid is also found in the central nervous system, synaptic system and other cellular membranes. Several epidemiological and *in vivo* studies have been shown that DHA has protective effects against AD and cognitive alterations. A study suggested that DHA have an antioxidant activity because it suppressed the increase in lipid peroxide and ROS levels in the cerebral cortex and hippocampus of the AD model rats (Hashimoto, Hossain *et al*. 2002, Cole and Frautschy 2006, De Wilde, Van Der Beek *et al.* 2010, Hashimoto, Hossain *et al.* 2015). Some experiments have demonstrated that DHA administration reduces amyloidogenic processing by decreasing β- and γ-secretase activity and increases the stability of α-secretase resulting in

increased non-amyloidogenic APP processing reduced amounts of $A\beta_{1-42}$ (Lim, Calon *et al.* 2005, Sahlin, Pettersson *et al.* 2007, Grimm, Kuchenbecker *et al.* 2011). In addition, DHA reduced the levels of Aβ oligomeric and at micellar concentrations stabilize soluble protofibrils hindering their conversion to insoluble fibrils through reducing of Aβ fibrillation (Johansson, Garlind *et al.* 2007, Hashimoto, Shahdat *et al.* 2008, Hashimoto, Shahdat *et al.* 2009, Hossain, Hashimoto *et al.* 2009). Results clearly indicated that DHA inhibited $A\beta_{1-42}$ fibril formation with a concomitant reduction in the levels of soluble $A\beta_{1-42}$ oligomers. The polymerization into fibrils of preformed oligomers treated with DHA was inhibited, indicating that DHA not only obstructs their formation but also inhibits their transformation into fibrils (Hossain, Hashimoto *et al.* 2009). Image analysis of brain sections revealed that overall plaque burden was significantly reduced in 40.3%, with the largest reductions (40-50%) in the hippocampus and parietal cortex (Lim, Calon *et al.* 2005). Besides that, DHA reduces the secreted Aβ levels and increases Aβ degradation (De Wilde, Van Der Beek *et al.* 2010, Hashimoto, Hossain *et al.* 2015) by affecting insulin-degrading enzyme, the major Aβ-degrading enzyme secreted into the extracellular space of neuronal and microglial cells (Grimm, Mett *et al.* 2016).

Epigallocatechin gallate: Epigallocatechin gallate (EGCG) is a major polyphenolic compound present in green tea (*Camellia sinensis*). Several studies have proved that EGCG exerts neuroprotective actions. Studies showed that EGCG promotes cleavage of αAPP, increasing in six times the αAPP release. These cleavage events are associated with elevated α-secretase activity and decreases β- and γ-secretase activities, which lead to the reduction of Aβ levels and plaques in brain (Jeon, Bae *et al*. 2003, Rezai-Zadeh, Shytle *et al.* 2005, Rezai-Zadeh, Shytle *et al*. 2005, Shimmyo, Kihara *et al*. 2008, Lee, Lee *et al*. 2009, Lee, Yuk *et al.* 2009, Zhang, Li *et al*. 2017). Moreover, EGCG inhibited the Aβ fibrillation *in vitro* by directly binding to the natively unfolded polypeptides and preventing their conversion into toxic species (Ehrnhoefer, Bieschke *et al*. 2008). In addition, EGCG inhibited Aβ oligomerization in transgenic *Caenorhabditis elegans* and fibril formation, disassembles preformed Aβ fibrils, converting large and mature Aβ fibrils into smaller and modulates tau hyperphosphorylation in transgenic mice (Rezai-Zadeh, Arendash *et al*. 2008, Hauber,

Hohenberg *et al*. 2009, Abbas and Wink 2010, Harvey, Musgrave *et al.* 2011). EGCG has the ability to inhibits the aggregation of tau into toxic oligomers and to increases the clearance of phosphorylated tau species (Wobst, Sharma *et al.* 2015, Chesser, Ganeshan *et al*. 2016). Lastly, EGCG has also been reported to exhibit potent antioxidant (Jeong, Kim *et al.* 2004, Kim, Lee *et al.* 2009, Biasibetti, Tramontina *et al.* 2013, Zhang, Li *et al.* 2017) and anti-inflammatory properties (Lee, Yuk *et al*. 2009, Lee, Choi *et al.* 2013, Cheng-Chung Wei, Huang *et al.* 2016).

Ferulic acid: Ferulic acid is a ubiquitous phenolic compound found in several fruits and vegetables. Ferulic acid is a naturally occurring antioxidants useful in therapeutic methodology against AD (Kanski, Aksenova *et al.* 2002, Kanski, Aksenova *et al.* 2002, Picone, Nuzzo *et al.* 2013, Maruf, Lip *et al.* 2015, Tsai, Wu *et al.* 2015, Shen, Zhang *et al.* 2016). Ferulic acid has the ability to inhibit Aβ production through the decreasing of β-secretase activity reducing amyloidogenic APP proteolysis (Ono, Hirohata *et al*. 2005, Mori, Koyama *et al.* 2013). The inhibition of the β-sheets that are required for the $A\beta_{1-42}$ monomer-to-oligomer transition was also observed, inhibiting the $A\beta_{1-42}$ aggregation (Cui, Zhang *et al.* 2013, Zhang, Cui *et al.* 2013). Amyloid deposition was also reduced with ferulic acid in a transgenic amyloid precursor protein (APP)swe/presenilin 1 (PS1)dE9 (APP/PS1) mouse model of AD (Yan, Jung *et al.* 2013). Besides, this compound destabilized and disrupted preformed Aβ fibrils (Ono, Hirohata *et al.* 2005).

Fisetin: Fisetin is a flavonoid found in plants such as the Japanese fruit wax tree (*Rhus succedanea*), and in very small amounts in strawberries, tomatoes, onions and other foods. This compound has been reported as inhibitor of Aβ aggregation, thereby inhibiting Aβ fibril formation (Akaishi, Morimoto *et al.* 2008, Akaishi, Morimoto *et al.* 2008). Treatment of cortical cells or primary neurons with fisetin resulted in significant decreases in the levels of phosphorylated tau (Kim, Choi *et al.* 2016). Furthermore, fisetin has been suggested as an antioxidant and anti-inflammatory which makes this flavonoid an important compound for the AD prevention (Zheng, Ock *et al.* 2008, Maher 2009, Ahmad, Ali *et al.* 2017).

Galantamine: Galantamine is produced by *Galanthus woronowii* Losinsk., some species of *Narcissus* and *Leucojum aestivum.* A study showed that galantamine may be

implicated in modifying AD pathophysiological mechanisms by reduces Aβ deposition, neuroinflammation, inhibiting Aβ aggregation, and facilitating Aβ clearance (Matharu, Gibson *et al*. 2009, Takata, Kitamura *et al.* 2010, Wu, Zhao *et al.* 2015). Antioxidant activity of galantamine was also proven (Melo, Sousa *et al.* 2009, Tsvetkova, Obreshkova *et al.* 2013). Results strongly support that galantamine improves cognitive and behavioral symptoms in AD due to its capacity to delay Aβ plaque formation in an AD mouse model (5XFAD) (Bhattacharya, Haertel *et al.* 2014). Additionally, galantamine binding to Aβ peptide dimer leads to a significant conformational change that disrupts interactions between individual β-strands and promotes a nontoxic conformation of Aβ to prevent the formation of neurotoxic oligomers (Rao, Mohamed *et al.* 2013). On the other hand, galantamine reduces Aβ production by inhibiting β-secretase, stimulating the non-amyloidogenic pathway (Li, Wu *et al.* 2010).

Gallic acid: Gallic acid is a type of phenolic acid found in a variety of foods and herbs. Gallic acid is the major component of grape seed extract. The use of gallic acid can improve spatial learning and memory impairment for several reasons. The first reason is that gallic acid has antioxidant and anti-inflammatory properties (Kim, Seong *et al.* 2011, Mansouri, Farbood *et al.* 2013, Mansouri, Naghizadeh *et al*. 2013, Hajipour, Sarkaki *et al*. 2016). Further, gallic acid inhibits fibril formation through the promotion of the non-amyloidogenic pathway by the increase of α-secretase activity and inhibits Aβ oligomerization (Valizadeh, Eidi *et al.* 2012, Liu, Pukala *et al.* 2013, Jayamani and Shanmugam 2014, Hajipour, Sarkaki *et al*. 2016).

Huperzine A: Huperzine A, an alkaloid extract from *Huperazia serrata* is an antioxidant due to their ability to inhibit ROS formation and reduce lipid peroxidation (Xiao, Wang *et al.* 2000, Xiao, Zhang *et al.* 2002, Xiao, Zhang *et al.* 2002). A study demonstrated that huperzine A increases αAPPs release, suggesting an increase in APP metabolism toward the non-amyloidogenic pathway. This result suggests that huperzine A has a modulatory effect on α-secretase activity (Peng, Jiang *et al.* 2006, Peng, Lee *et al.* 2007). As a consequence, the Aβ level decrease significantly, suggesting an inhibitory effect of Huperzine A in Aβ production (Peng, Jiang *et al.* 2006).

Kaempferol: Kaempferol is a natural polyphenolic flavonoid founded in a variety of fruits, vegetables, wine and tea. Studies have shown that kaempferol acts as antioxidant and anti-inflammatory (Marfak, Trouillas *et al.* 2003, Garcia-Mediavilla, Crespo *et al.* 2007). One study showed that kaempferol inhibits the formation of Aβ fibrils as well as their extension and destabilizes preformed Aβ fibrils (Ono, Yoshiike *et al*. 2003). Probably, the inhibition of Aβ fibrils formation is caused by their capacity to inhibit Aβ aggregation (Akaishi, Morimoto *et al.* 2008). Another study reported that kaempferol is a β-secretase inhibitor (Shimmyo, Kihara *et al.* 2008). For these reasons, this polyphenol could be a key molecule for the development of preventives and therapeutics for AD.

Luteolin: Luteolin is a natural polyphenol flavonoid that exists in many types of plants including fruits, vegetables, and medicinal herbs. Accumulating evidence has shown that luteolin exhibit potent anti-inflammatory properties and antioxidant mechanisms that protect against oxidative stress (Pavlica and Gebhardt 2010, Zhu, Bi *et al.* 2011, Zhao, Yao-Yue *et al.* 2012, Zhang, Xing *et al*. 2017). An experimental study discovered that luteolin is a potent inhibitor of β-secretase. Until the date, it is one of the most potent natural product inhibitors of β-secretase (Choi, Hur *et al.* 2008, Zheng, Yuan *et al.* 2015). Another study revealed that luteolin is able to regulate tau hyperphosphorylation (Zhou, Chen *et al.* 2012).

Melatonin: Melatonin is an alkaloid found in animals, plants, fungi and bacteria. A number of experiments have shown that melatonin is a potent antioxidant due to their ability in neutralize oxygen-derived free radicals, reduce ROS production and scavenge species of other types such as carbon-centered free radicals (Daniels, van Rensburg *et al.* 1998, Pappolla, Chyan *et al*. 2000, Clapp-Lilly, Smith *et al*. 2001, Matsubara, Bryant-Thomas *et al.* 2003, Feng, Qin *et al.* 2006, Gunasingh, Philip *et al.* 2008). In addition, a study reported the beneficial effects of melatonin on inflammation (Jesudason, Baben *et al.* 2007). Farther, melatonin has been described as an anti-aggregation agent. A study demonstrated that melatonin inhibits the progressive formation of β-sheets and amyloid fibrils, decreasing the $A\beta_{1-42}$ and $A\beta_{1-40}$ levels in the rat brains (Pappolla, Bozner *et al.* 1998, Poeggeler, Miravalle *et al.* 2001, Rudnitskaya, Muraleva *et al.* 2015). Another investigation affirmed that melatonin inhibits β- and γ-

secretase activity and PS1/PS2 but also actives the α-secretase expression thereby favoring the non-amyloidogenic pathway (Panmanee, Nopparat *et al.* 2015).

Myricetin: Myricetin is a naturally occurring flavonoid found in many grapes, berries, fruits, vegetables, and herbs as well as other plants. This compound is classified as a strong antioxidant. Evidences revealed that myricetin is an antioxidant that prevented the formation of Aβ aggregates, as well as their extension, with a persistent level of monomes (Shimmyo, Kihara *et al.* 2008, Fiori, Naldi *et al.* 2012). These effects were based on two mechanisms: the activation and up-regulation of α-secretase and the inhibition of β-secretase (Shimmyo, Kihara *et al.* 2008). A high inhibitory effect of myricetin on fibrillogenesis of Aβ was also observed. A study demonstrated an anti-amyloidogenic effect through the reversible binding of myricetin to fibrillar Aβ, but not to the monomeric species, causing Aβ conformational changes (Hirohata, Hasegawa *et al.* 2007). Additionally, this compound destabilized preformed Aβ fibrils (Ono, Yoshiike *et al.* 2003).

Nicotine: Nicotine is an alkaloid isolated from the leaves of tobacco plant (*Nicotiana tabacum*) that affects multiple stages of amyloidogenesis *in vitro*. A study reported that nicotine may effectively reduce Aβ aggregation in brain, inhibiting the formation and extension of Aβ fibrils, and it was able to destabilize preformed Aβ fibrils, causing a significantly reduction of Aβ levels and plaque levels by more than 80% (Nordberg, Hellstrom-Lindahl *et al.* 2002, Ono, Hasegawa *et al.* 2002, Srivareerat, Tran *et al.* 2011). This reduction can be due to the decrease of APP (Lahiri, Utsuki *et al.* 2002, Utsuki, Shoaib *et al.* 2002). Nicotine retards amyloidogenesis by preventing an α-helix to β-sheet conformational transformation, decreasing β-secretase and PSEN1 expression (Salomon, Marcinowski *et al.* 1996, Nie, Li *et al.* 2011, Srivareerat, Tran *et al.* 2011, Alkadhi, Alzoubi *et al.* 2012). In addition to the reasons mentioned above, a different study suggests that the beneficial/protective effects of nicotine in AD may be, at least partly, due to antioxidant mechanisms (Linert, Bridge *et al.* 1999).

Puerarin: Puerarin, an isoflavanone glycoside extracted from the dried roots of *Pueraria lobata,* has been reported to be useful in the treatment of various diseases. Studies found that puerarin had potent effects in improving spatial learning and memory

by inhibiting the phosphorylation of tau in APP/PS1 double transgenic mice (Xu 2003, Zhou, Xie *et al.* 2014, Zhao, Yang *et al.* 2015, Mei, Tan *et al.* 2016). The anti-AD effects of puerarin suggested to be related to its abilities to decrease the oxidative stress and the neuroinflammation associated with AD (Jiang, Liu *et al.* 2003, Mahdy, Mohamed *et al.* 2014, Zhou, Xie *et al.* 2014, Zhao, Yang *et al.* 2015).

Quercetin: Quercetin is a flavonol founded in fruits, vegetables, herbs, tea, and wine. Studies showed that quercetin decreased oxidative stress by the strong decrease of ROS generation and the index of lipid peroxidation (Heo and Lee 2004, Jimenez-Aliaga, Bermejo-Bescos *et al.* 2011, Ademosun, Oboh *et al.* 2016). Moreover, quercetin disaggregated Aβ fibrils, transforming the fibrils into amorphous aggregates (Wang, Wang *et al.* 2011). Quercetin, by specifically activating macroautophagy and proteasomal degradation pathways, proved to be able to prevent $A\beta_{1\text{-}42}$ aggregation, inhibiting the formation of Aβ fibrils and reducing brain Aβ levels in amyloid model mice (5xFAD) (Jimenez-Aliaga, Bermejo-Bescos *et al.* 2011, Regitz, Dussling *et al.* 2014, Zhang, Hu *et al.* 2016). Additionally, this compound is a natural β-secretase inhibitor (approximately 20–30%) and can attenuate tau hyperphosphorylation (Shimmyo, Kihara *et al.* 2008, Chen, Deng *et al.* 2016).

Resveratrol: Resveratrol is a natural non-flavonoid polyphenol founded in high concentrations in grapes (*Vitis vinifera* L. (Vitaceae)). Studies showed that resveratrol markedly slow down the formation of Aβ fibrils and their extension by disrupting $A\beta_{1\text{-}42}$ hydrogen bonding and promote intracellular degradation of Aβ aggregates and preformed $A\beta_{1\text{-}42}$ fibrils *in vitro* through promotion of intracellular proteosomal activity (Marambaud, Zhao *et al*. 2005, Feng, Wang *et al.* 2009). Also *in vitro* studies showed that resveratrol interfere in $A\beta_{1\text{-}42}$ aggregation, retarding or even inhibiting the aggregation of Aβ, and change the $A\beta_{1\text{-}42}$ oligomers conformation (Feng, Wang *et al*. 2009, Loureiro, Andrade *et al.* 2017). Resveratrol selectively remodels three of conformers (soluble oligomers, fibrillar intermediates, and amyloid fibrils) into an alternative aggregated species that are non-toxic, high molecular weight, and unstructured (Ladiwala, Lin *et al.* 2010). Besides that, resveratrol reduced the insoluble $A\beta_{1\text{-}42}$ level in hippocampus and plaque formation in medial cortex (-48%), striatum (-89%) and hypothalamus (-90%) (Karuppagounder, Pinto *et al.* 2009, Zhao, Li *et al.*

2015). A study suggests that resveratrol reduces the Aβ levels by promoting a non-amyloidogenic processing of APP (Marambaud, Zhao *et al.* 2005). In addition, resveratrol exerts anti-inflammatory and antioxidant effects (Fremont 2000, Kumar, Naidu *et al.* 2007, de Almeida, Leite *et al*. 2008, Gong, Li *et al.* 2010, Lu, Ma *et al.* 2010, Ma, Sun *et al.* 2013, Rege, Geetha *et al*. 2015, Moussa, Hebron *et al.* 2017). Specifically, it scavenges ROS and up-regulates cellular antioxidants including glutathione (Jang and Surh 2003, Granzotto and Zatta 2011). Lastly, resveratrol can inhibits tau hyperhosphorylation (He, Li *et al.* 2017).

Retinoic acid: In similarity with retinal, retinoic acid is also a naturally occurring terpenoid, a metabolite of vitamin A reported to have anti-aggregation activity and Aβ fibrils clearance activity (Ono, Yoshiike *et al.* 2004). Retinoic acid can suppress the production of Aβ through direct inhibition of β- and γ-secretase activity and the promotion of α-secretase activity (Koryakina, Aeberhard *et al.* 2009, Tippmann, Hundt *et al.* 2009, Kapoor, Wang *et al*. 2013).

Salvianolic acid B: Salvianolic acid B is a phenylpropanol isolated from the root of *Salvia miltiorrhiza,* a Chinese herbal medicine. Salvianolic acid B is a promising agent in treatment of neurodegenerative diseases. Studies demonstrated that salvianolic acid B is a potent natural antioxidant, which could scavenge superoxide anion, ROS and hydroxyl radicals and inhibit lipid peroxidation (Huang and Zhang 1992). This compound can significantly suppress the accumulation of Aβ, inhibit Aβ aggregation, thereby preventing the formation of Aβ and disaggregate Aβ fibrils (Tang and Zhang 2001, Durairajan, Yuan *et al.* 2008, Cheng, Gong *et al.* 2013). A study suggests that salvianolic acid B is a promising therapeutic agent for AD by inhibiting Aβ generation by suppressing β-secretase (Tang, Huang *et al.* 2016).

Vitamin C: The richest natural sources of vitamin C are fruits and vegetables, and of those, the Kakadu plum and the camu camu fruit contain the highest concentration. Data showed that individuals with lower plasma vitamin C values are at high risk for developing AD (Helmer, Peuchant *et al.* 2003). Several studies conducted in mice reported that vitamin C prevented brain oxidative damage through their potent antioxidant activity for neutralizing free radicals (Tabet, Mantle *et al.* 2002, Choi,

Conrad *et al.* 2003, Martin 2003, Ho and Chang 2004, Sil, Ghosh *et al.* 2016). A study reported that vitamin C attenuated Aβ oligomers formation and behavioral decline in an AD mouse model. The attenuation of Aβ oligomerization was accompanied with a marked decrease in the ratio of soluble $A\beta_{1-42}$ to $A\beta_{1-40}$ (Murakami, Murata *et al.* 2011). In addition, the high supplementation of vitamin C resulted in the reduction of Aβ plaque burden in the cortex and hippocampus in mice with AD (Kook, Lee *et al.* 2014).

Vitamin E: The vitamin E is present in several fruits and vegetables including wheat germ and almond oils. It was observed that the risk for developing AD increases in individual with lower plasma vitamin E values (Helmer, Peuchant *et al.* 2003). Studies showed that vitamin E acts as a major chain-breaking lipid soluble antioxidant responsible for blocking lipidic peroxidation. It also appears to have the function of scavenging free Aβ-associated radicals (Subramaniam, Koppal *et al.* 1998, Butterfield, Koppal *et al.* 1999, Yatin, Yatin *et al.* 1999). Conducted trials in mice proved that pretreatment with vitamin E prevented brain oxidative damage (Choi, Conrad *et al.* 2003, Giraldo, Lloret *et al.* 2014). Besides that, vitamin E possesses anti-inflammatory activity (Rosales-Corral, Tan *et al.* 2003). Other study using a transgenic model of AD (Tg2576) revealed that when vitamin E was administered at a young age showed a significant reduction in Aβ levels and amyloid deposition, reducing neuronal injuries (Sung, Yao *et al.* 2004, Kong, Yao *et al.* 2007).

Table 1 - Natural products with neurological activities, their typical origin and their mode of action.

Compound	Typical origin	Mechanism of action
Apigenin	*Matricaria chamomilla*	Antioxidant; Anti-inflammatory; Inhibition of β-secretase; Inhibition of Aβ deposition
Asiatic acid	*Centella asiatica*	Antioxidant; Inhibition of β-secretase; Activation of α-secretase; Aβ clearance
Baicalein	*Scutellaria baicalensis*	Antioxidant; Activation of α-secretase; Inhibition of β-secretase; Inhibition of Aβ fibrillation, Aβ oligomerization and Aβ aggregation; Clearance of Aβ fibrils; Inhibition of tau hyperphosphorylation
Berberine	*Rhizoma coptidis*	Antioxidant; Anti-inflammatory; Inhibition of β-secretase; Aβ clearance; Inhibition of tau hyperphosphorylation
Caffeine	Coffee bean	Antioxidant; Anti-inflammatory; Inhibition of β and γ-secretase; Aβ clearance; Inhibitor of β-sheet formation; Inhibitor of tau hyperphosphorylation
Colostrinin	Colostrum	Antioxidant; Anti-inflammatory; Inhibition of Aβ aggregation; Clearance of Aβ aggregates
Crocin	*Crocus sativus*	Antioxidant; Anti-inflammatory; Inhibition of Aβ fibrils formation; Clearance of Aβ aggregates
Curcumin	*Curcuma longa*	Antioxidant; Anti-inflammatory; Inhibition of β-and γ-secretase; Inhibition of Aβ fibrillation; Inhibition of Aβ aggregation; Inhibition of Aβ fibril formation; Inhibition of Aβ plaques formation; Clearance of Aβ fibrils; Inhibition of tau hyperphosphorylation

Compound	Typical origin	Mechanism of action
Docosahexaenoic acid	Marine fish and algae	Antioxidant; Inhibition of β- and γ-secretase; Activation of α-secretase; Inhibition of Aβ fibril formation, Aβ fibrillation and Aβ oligomerization; Aβ degradation
Epigallocatechin gallate	*Camellia sinensis*	Antioxidant; Anti-inflammatory; Inhibition of β- and γ-secretase; Activation of α-secretase; Inhibition of Aβ fibrillation and Aβ oligomerization; Clearance of Aβ fibrils; Inhibition of tau hyperphosphorylation; Inhibition of tau aggregation; Clearance of tau fibrils
Ferulic acid	*Ferula communis*	Antioxidant; Inhibition of β-secretase; Inhibition of Aβ fibrillation and Aβ aggregation; Clearance of Aβ fibrils
Fisetin	*Rhus succedanea*	Antioxidant; Anti-inflammatory; Inhibition of Aβ aggregation; Inhibition of Aβ fibril formation
Galantamine	*Galanthus woronowii* Losinsk.	Antioxidant; Anti-inflammatory; Inhibition of β-secretase; Inhibition of Aβ deposition; Inhibition of Aβ aggregation; Inhibition of Aβ plaque formation; Aβ clearance
Gallic acid	*Camellia sinensis*	Antioxidant; Anti-inflammatory; Activation of α-secretase; Inhibition of Aβ oligomerization
Huperzine A	*Huperazia serrata*	Antioxidant; Activation of α-secretase
Kaempferol	*Camellia sinensis*	Antioxidant; Anti-inflammatory; Inhibition of β-secretase; Inhibition of Aβ aggregation; Clearance of Aβ fibrils
Luteolin	*Perilla frutescens*	Antioxidant; Anti-inflammatory; Inhibition of β-secretase; Inhibition of tau hyperphosphorylation

Compound	Typical origin	Mechanism of action
Melatonin	Pineal glands	Antioxidant; Anti-inflammatory; Inhibition of β- and γ-secretase; Activation of α-secretase; Inhibition of Aβ aggregation and Aβ fibrillation
Myricetin	*Myristica fragrans*	Antioxidant; Inhibition of β-secretase; Activation of α-secretase; Inhibition of Aβ fibrillation; Clearance of Aβ fibrils
Nicotine	*Nicotiana tabacum*	Antioxidant; Inhibition of β-secretase; Inhibition of Aβ aggregation and β-sheet formation; Clearance of Aβ fibrils
Puerarin	*Pueraria lobata*	Antioxidant; Anti-inflammatory; Inhibition of tau hyperphosphorylation
Quercetin	Apple	Antioxidant; Inhibition of β-secretase; Inhibition of Aβ aggregation; Clearance of Aβ fibrils; Inhibition of tau hyperphosphorylation
Resveratrol	*Vitis vinifera*	Antioxidant; Anti-inflammatory; Activation of α-secretase; Inhibition of Aβ aggregation; Inhibition of Aβ conformation; Clearance of Aβ; Inhibition of tau hyperphosphorylation
Retinoic acid	Carotenoids	Inhibition of β- and γ-secretase; Activation of α-secretase; Inhibition of Aβ aggregation; Clearance of Aβ fibrils
Salvianolic acid B	*Salvia miltiorrhiza*	Antioxidant; Inhibition of β-secretase; Inhibition of Aβ accumulation; Inhibition of Aβ aggregation; Clearance of Aβ fibrils
Vitamin C	Kakadu plum	Antioxidant; Inhibition of Aβ oligomers formation
Vitamin E	Wheat germ oil	Antioxidant; Anti-inflammatory

IV. Conclusions

AD is known as the most important neurodegenerative disease and the most common cause of dementia among the elderly. This disease is multifactorial and incapacitating that deprives patients of basic cognitive functions, culminating in a state of dementia and complete loss of independence. At the moment, no pharmacologically effective treatment to stop or cure the progression of AD has been developed. With the increase of average life expectancy, the discovery and development of new drugs to treat AD is highly demanding.

The potential of natural products for the prevention and cure of AD is supported by the literature. The majority of natural compounds studied to date with a direct relevance to AD are mainly from plants, with comparatively few molecules derived from marine and microbial sources. As multiple causative factors exist for the pathology of AD, various mechanisms may be associated with the preventative effects and treatment. Most of these natural products are rich in polyphenols and have been preferably studied due to their multiple functions (such antioxidant and anti-inflammatory properties). Therefore, in this document was proved that natural products are promising for the future treatment of AD.

V. References

Abbas, S. and M. Wink (2010). "Epigallocatechin gallate inhibits beta amyloid oligomerization in Caenorhabditis elegans and affects the daf-2/insulin-like signaling pathway." Phytomedicine **17**(11): 902-909.

Abd El-Wahab, A. E., D. A. Ghareeb, E. E. M. Sarhan, M. M. Abu-Serie and M. A. El Demellawy (2013). "In vitro biological assessment of berberis vulgaris and its active constituent, berberine: Antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects." BMC Complementary and Alternative Medicine **13**.

Ademosun, A. O., G. Oboh, F. Bello and P. O. Ayeni (2016). "Antioxidative Properties and Effect of Quercetin and Its Glycosylated Form (Rutin) on Acetylcholinesterase and Butyrylcholinesterase Activities." Journal of Evidence-Based Complementary and Alternative Medicine **21**(4): NP11-NP17.

Aggarwal, B. B., A. Kumar and A. C. Bharti (2003). "Anticancer potential of curcumin: preclinical and clinical studies." Anticancer Res **23**(1A): 363-398.

Ahmad, A., T. Ali, H. Y. Park, H. Badshah, S. U. Rehman and M. O. Kim (2017). "Neuroprotective Effect of Fisetin Against Amyloid-Beta-Induced Cognitive/Synaptic Dysfunction, Neuroinflammation, and Neurodegeneration in Adult Mice." Molecular Neurobiology **54**(3): 2269-2285.

Ahmed, M., J. Davis, D. Aucoin, T. Sato, S. Ahuja, S. Aimoto, J. I. Elliott, W. E. Van Nostrand and S. O. Smith (2010). "Structural conversion of neurotoxic amyloid-beta(1-42) oligomers to fibrils." Nat Struct Mol Biol **17**(5): 561-567.

Aisen, P. S. (2002). "The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease." Lancet Neurol **1**(5): 279-284.

Ak, T. and I. Gulcin (2008). "Antioxidant and radical scavenging properties of curcumin." Chem Biol Interact **174**(1): 27-37.

Akaishi, T., T. Morimoto, M. Shibao, S. Watanabe, K. Sakai-Kato, N. Utsunomiya-Tate and K. Abe (2008). "Structural requirements for the flavonoid fisetin in inhibiting fibril formation of amyloid beta protein." Neurosci Lett **444**(3): 280-285.

Akaishi, T., T. Morimoto, M. Shibao, S. Watanabe, K. Sakai-Kato, N. Utsunomiya-Tate and K. Abe (2008). "Structural requirements for the flavonoid fisetin in inhibiting fibril formation of amyloid β protein." Neuroscience Letters **444**(3): 280-285.

Alkadhi, K. A., K. H. Alzoubi, M. Srivareerat and T. T. Tran (2012). "Elevation of BACE in an Aβ rat model of Alzheimer's disease: Exacerbation by chronic stress and prevention by nicotine." International Journal of Neuropsychopharmacology **15**(2): 223-233.

Alves, L., A. S. Correia, R. Miguel, P. Alegria and P. Bugalho (2012). "Alzheimer's disease: a clinical practice-oriented review." Front Neurol **3**: 63.

Alzheimer, A., R. A. Stelzmann, H. N. Schnitzlein and F. R. Murtagh (1995). "An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde"." Clin Anat **8**(6): 429-431.

Arendash, G. W., T. Mori, C. Cao, M. Mamcarz, M. Runfeldt, A. Dickson, K. Rezai-Zadeh, J. Tan, B. A. Citron, X. Lin, V. Echeverria and H. Potter (2009). "Caffeine reverses cognitive impairment and decreases brain amyloid-β levels in aged alzheimer's disease mice." Journal of Alzheimer's Disease **17**(3): 661-680.

Arendash, G. W., T. Mori, C. Cao, M. Mamcarz, M. Runfeldt, A. Dickson, K. Rezai-Zadeh, J. Tane, B. A. Citron, X. Lin, V. Echeverria and H. Potter (2009). "Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice." J Alzheimers Dis **17**(3): 661-680.

Arendash, G. W., W. Schleif, K. Rezai-Zadeh, E. K. Jackson, L. C. Zacharia, J. R. Cracchiolo, D. Shippy and J. Tan (2006). "Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production." Neuroscience **142**(4): 941-952.

Arendt, T. (2009). "Synaptic degeneration in Alzheimer's disease." Acta Neuropathol **118**(1): 167-179.

Arriagada, P. V., J. H. Growdon, E. T. Hedley-Whyte and B. T. Hyman (1992). "Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease." Neurology **42**(3 Pt 1): 631-639.

Asai, M., N. Iwata, A. Yoshikawa, Y. Aizaki, S. Ishiura, T. C. Saido and K. Maruyama (2007). "Berberine alters the processing of Alzheimer's amyloid precursor protein to decrease Abeta secretion." Biochem Biophys Res Commun **352**(2): 498-502.

Balez, R., N. Steiner, M. Engel, S. S. Munoz, J. S. Lum, Y. Wu, D. Wang, P. Vallotton, P. Sachdev, M. O'Connor, K. Sidhu, G. Munch and L. Ooi (2016). "Neuroprotective effects of apigenin against inflammation, neuronal excitability and apoptosis in an induced pluripotent stem cell model of Alzheimer's disease." Sci Rep **6**: 31450.

Ballard, C., S. Gauthier, A. Corbett, C. Brayne, D. Aarsland and E. Jones (2011). "Alzheimer's disease." Lancet **377**(9770): 1019-1031.

Barage, S. H. and K. D. Sonawane (2015). "Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease." Neuropeptides **52**: 1-18.

Bard, F., C. Cannon, R. Barbour, R. L. Burke, D. Games, H. Grajeda, T. Guido, K. Hu, J. Huang, K. Johnson-Wood, K. Khan, D. Kholodenko, M. Lee, I. Lieberburg, R. Motter, M. Nguyen, F. Soriano, N. Vasquez, K. Weiss, B. Welch, P. Seubert, D. Schenk and T. Yednock (2000). "Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease." Nat Med **6**(8): 916-919.

Bates, K. A., G. Verdile, Q. X. Li, D. Ames, P. Hudson, C. L. Masters and R. N. Martins (2009). "Clearance mechanisms of Alzheimer's amyloid-beta peptide: implications for therapeutic design and diagnostic tests." Mol Psychiatry **14**(5): 469-486.

Bend, J. R., X. Y. Xia, D. Chen, A. Awaysheh, A. Lo, M. J. Rieder and R. Jane Rylett (2015). "Attenuation of oxidative stress in HEK 293 cells by the TCM constituents schisanhenol, baicalein, resveratrol or crocetin and two defined mixtures." Journal of Pharmacy and Pharmaceutical Sciences **18**(4): 661-682.

Bhattacharya, S., C. Haertel, A. Maelicke and D. Montag (2014). "Galantamine slows down plaque formation and behavioral decline in the 5XFAD mouse model of Alzheimer's disease." PLoS ONE **9**(2).

Biasibetti, R., A. C. Tramontina, A. P. Costa, M. F. Dutra, A. Quincozes-Santos, P. Nardin, C. L. Bernardi, K. M. Wartchow, P. S. Lunardi and C. A. Gonçalves (2013). "Green tea (-)epigallocatechin-3-gallate reverses oxidative stress and reduces acetylcholinesterase activity in a streptozotocin-induced model of dementia." Behavioural Brain Research **236**(1): 186-193.

Blennow, K., M. J. de Leon and H. Zetterberg (2006). "Alzheimer's disease." Lancet **368**(9533): 387-403.

Boldogh, I. and M. L. Kruzel (2008). "Colostrinin: an oxidative stress modulator for prevention and treatment of age-related disorders." J Alzheimers Dis **13**(3): 303-321.

Bourhim, M., M. Kruzel, T. Srikrishnan and T. Nicotera (2007). "Linear quantitation of Aβ aggregation using Thioflavin T: Reduction in fibril formation by colostrinin." Journal of Neuroscience Methods **160**(2): 264-268.

Brendza, R. P., B. J. Bacskai, J. R. Cirrito, K. A. Simmons, J. M. Skoch, W. E. Klunk, C. A. Mathis, K. R. Bales, S. M. Paul, B. T. Hyman and D. M. Holtzman (2005). "Anti-Abeta antibody treatment promotes the rapid recovery of amyloid-associated neuritic dystrophy in PDAPP transgenic mice." J Clin Invest **115**(2): 428-433.

Brookmeyer, R., E. Johnson, K. Ziegler-Graham and H. M. Arrighi (2007). "Forecasting the global burden of Alzheimer's disease." Alzheimers Dement **3**(3): 186-191.

Brothers, H. M., Y. Marchalant and G. L. Wenk (2010). "Caffeine attenuates lipopolysaccharide-induced neuroinflammation." Neuroscience Letters **480**(2): 97-100.

Butterfield, D. A., T. Koppal, R. Subramaniam and S. Yatin (1999). "Vitamin E as an antioxidant/free radical scavenger against amyloid β-peptide-induced oxidative stress in neocortical synaptosomal membranes and hippocampal neurons in culture: Insights into Alzheimer's disease." Reviews in the Neurosciences **10**(2): 141-149.

Butterfield, D. A., T. Reed, S. F. Newman and R. Sultana (2007). "Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment." Free Radical Biology and Medicine **43**(5): 658-677.

Buttini, M., E. Masliah, R. Barbour, H. Grajeda, R. Motter, K. Johnson-Wood, K. Khan, P. Seubert, S. Freedman, D. Schenk and D. Games (2005). "Beta-amyloid immunotherapy prevents synaptic degeneration in a mouse model of Alzheimer's disease." J Neurosci **25**(40): 9096-9101.

Caesar, I., M. Jonson, K. P. R. Nilsson, S. Thor and P. Hammarström (2012). "Curcumin promotes a-beta fibrillation and reduces neurotoxicity in transgenic Drosophila." PLoS ONE **7**(2).

Cao, C., J. R. Cirrito, X. Lin, L. Wang, D. K. Verges, A. Dickson, M. Mamcarz, C. Zhang, T. Mori, G. W. Arendash, D. M. Holtzman and H. Potter (2009). "Caffeine suppresses amyloid-β levels in plasma and brain of alzheimer's disease transgenic mice." Journal of Alzheimer's Disease **17**(3): 681-697.

Castellani, R. J., R. K. Rolston and M. A. Smith (2010). "Alzheimer disease." Dis Mon **56**(9): 484-546.

Chen, J., X. Deng, N. Liu, M. Li, B. Liu, Q. Fu, R. Qu and S. Ma (2016). "Quercetin attenuates tau hyperphosphorylation and improves cognitive disorder via suppression of ER stress in a manner dependent on AMPK pathway." Journal of Functional Foods **22**: 463-476.

Cheng, B., H. Gong, X. Li, Y. Sun, H. Chen, X. Zhang, Q. Wu, L. Zheng and K. Huang (2013). "Salvianolic acid B inhibits the amyloid formation of human islet amyloid polypeptide and protects pancreatic beta-cells against cytotoxicity." Proteins **81**(4): 613-621.

Cheng-Chung Wei, J., H. C. Huang, W. J. Chen, C. N. Huang, C. H. Peng and C. L. Lin (2016). "Epigallocatechin gallate attenuates amyloid β-induced inflammation and neurotoxicity in EOC 13.31 microglia." European Journal of Pharmacology **770**: 16-24.

Chesser, A. S., V. Ganeshan, J. Yang and G. V. W. Johnson (2016). "Epigallocatechin-3-gallate enhances clearance of phosphorylated tau in primary neurons." Nutritional Neuroscience **19**(1): 21-31.

Chirita, C., M. Necula and J. Kuret (2004). "Ligand-dependent inhibition and reversal of tau filament formation." Biochemistry **43**(10): 2879-2887.

Choi, J., C. C. Conrad, R. Dai, C. A. Malakowsky, J. M. Talent, C. A. Carroll, S. T. Weintraub and R. W. Gracy (2003). "Vitamin E prevents oxidation of antiapoptotic proteins in neuronal cells." Proteomics **3**(1): 73-77.

Choi, J. H., A. Y. Choi, H. Yoon, W. Choe, K. S. Yoon, J. Ha, E. J. Yeo and I. Kang (2010). "Baicalein protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress-induced apoptosis through inhibition of reactive oxygen species production and CHOP induction." Experimental and Molecular Medicine **42**(12): 811-822.

Choi, J. S., M. N. Islam, M. Y. Ali, E. J. Kim, Y. M. Kim and H. A. Jung (2014). "Effects of C-glycosylation on anti-diabetic, anti-Alzheimer's disease and anti-inflammatory potential of apigenin." Food and Chemical Toxicology **64**: 27-33.

Choi, S. H., J. M. Hur, E. J. Yang, M. Jun, H. J. Park, K. B. Lee, E. Moon and K. S. Song (2008). "Beta-secretase (BACE1) inhibitors from Perilla frutescens var. acuta." Arch Pharm Res **31**(2): 183-187.

Chu, Y. F., W. H. Chang, R. M. Black, J. R. Liu, P. Sompol, Y. Chen, H. Wei, Q. Zhao and I. H. Cheng (2012). "Crude caffeine reduces memory impairment and amyloid β1-42 levels in an Alzheimer's mouse model." Food Chemistry **135**(3): 2095-2102.

Citron, M. (2010). "Alzheimer's disease: strategies for disease modification." Nat Rev Drug Discov **9**(5): 387-398.

Clapp-Lilly, K. L., M. A. Smith, G. Perry, P. L. Harris, X. Zhu and L. K. Duffy (2001). "Melatonin acts as antioxidant and pro-oxidant in an organotypic slice culture model of Alzheimer's disease." NeuroReport **12**(6): 1277-1280.

Clark, C. M. and J. H. Karlawish (2003). "Alzheimer disease: current concepts and emerging diagnostic and therapeutic strategies." Ann Intern Med **138**(5): 400-410.

Clippingdale, A. B., J. D. Wade and C. J. Barrow (2001). "The amyloid-beta peptide and its role in Alzheimer's disease." J Pept Sci **7**(5): 227-249.

Cole, G. M. and S. A. Frautschy (2006). "Docosahexaenoic acid protects from amyloid and dendritic pathology in an Alzheimer's disease mouse model." Nutrition and Health **18**(3): 249-259.

Cui, L., Y. Zhang, H. Cao, Y. Wang, T. Teng, G. Ma, Y. Li, K. Li and Y. Zhang (2013). "Ferulic acid inhibits the transition of amyloid-beta42 monomers to oligomers but accelerates the transition from oligomers to fibrils." J Alzheimers Dis **37**(1): 19-28.

Cummings, J. L. (2004). "Alzheimer's disease." N Engl J Med **351**(1): 56-67.

Currais, A., K. Kato, L. Canuet, R. Ishii, T. Tanaka, M. Takeda and S. Soriano (2011). "Caffeine modulates tau phosphorylation and affects Akt signaling in postmitotic neurons." Journal of Molecular Neuroscience **43**(3): 326-332.

Daniels, W. M., S. J. van Rensburg, J. M. van Zyl and J. J. Taljaard (1998). "Melatonin prevents beta-amyloid-induced lipid peroxidation." J Pineal Res **24**(2): 78-82.

Das, S., P. M. Mazumder and S. Das (2015). "Antioxidant potential of methanol stem extract of Berberis aristata DC. and berberine- a bioactive compound isolated from Berberis aristata DC." International Journal of Pharma and Bio Sciences **6**(4): P349-P360.

de Almeida, L. M. V., M. C. Leite, A. P. Thomazi, C. Battu, P. Nardin, L. S. Tortorelli, C. Zanotto, T. Posser, S. T. Wofchuk, R. B. Leal, C. A. Gonçalves and C. Gottfried (2008). "Resveratrol protects against oxidative injury induced by H2O2 in acute hippocampal slice preparations from Wistar rats." Archives of Biochemistry and Biophysics **480**(1): 27-32.

De Wilde, M. C., E. M. Van Der Beek, A. J. Kiliaan, I. Leenders, A. A. M. Kuipers, P. J. Kamphuis and L. M. Broersen (2010). "Docosahexaenoic acid reduces amyloid-β 1-42 secretion in human AβPP-transfected CHO-cells by mechanisms other than inflammation related to PGE." Journal of Alzheimer's Disease **21**(4): 1271-1281.

Dhanasekaran, M., L. A. Holcomb, A. R. Hitt, B. Tharakan, J. W. Porter, K. A. Young and B. V. Manyam (2009). "Centella asiatica extract selectively decreases amyloid β levels in hippocampus of Alzheimer's disease animal model." Phytotherapy Research **23**(1): 14-19.

Du, Y., X. Wei, R. Dodel, N. Sommer, H. Hampel, F. Gao, Z. Ma, L. Zhao, W. H. Oertel and M. Farlow (2003). "Human anti-beta-amyloid antibodies block beta-amyloid fibril formation and prevent beta-amyloid-induced neurotoxicity." Brain **126**(Pt 9): 1935-1939.

Durairajan, S. S., Q. Yuan, L. Xie, W. S. Chan, W. F. Kum, I. Koo, C. Liu, Y. Song, J. D. Huang, W. L. Klein and M. Li (2008). "Salvianolic acid B inhibits Abeta fibril formation and disaggregates preformed fibrils and protects against Abeta-induced cytotoxicty." Neurochem Int **52**(4-5): 741-750.

Durairajan, S. S. K., L. F. Liu, J. H. Lu, L. L. Chen, Q. Yuan, S. K. Chung, L. Huang, X. S. Li, J. D. Huang and M. Li (2012). "Berberine ameliorates β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model." Neurobiology of Aging **33**(12): 2903-2919.

Ehrnhoefer, D. E., J. Bieschke, A. Boeddrich, M. Herbst, L. Masino, R. Lurz, S. Engemann, A. Pastore and E. E. Wanker (2008). "EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers." Nat Struct Mol Biol **15**(6): 558-566.

Eriksen, J. L., S. A. Sagi, T. E. Smith, S. Weggen, P. Das, D. C. McLendon, V. V. Ozols, K. W. Jessing, K. H. Zavitz, E. H. Koo and T. E. Golde (2003). "NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo." J Clin Invest **112**(3): 440-449.

Fahrenholz, F. (2007). "Alpha-secretase as a therapeutic target." Curr Alzheimer Res **4**(4): 412-417.

Feng, Y., X. P. Wang, S. G. Yang, Y. J. Wang, X. Zhang, X. T. Du, X. X. Sun, M. Zhao, L. Huang and R. T. Liu (2009). "Resveratrol inhibits beta-amyloid oligomeric cytotoxicity but does not prevent oligomer formation." Neurotoxicology **30**(6): 986-995.

Feng, Z., C. Qin, Y. Chang and J. T. Zhang (2006). "Early melatonin supplementation alleviates oxidative stress in a transgenic mouse model of Alzheimer's disease." Free Radical Biology and Medicine **40**(1): 101-109.

Finley, J. W. and S. Gao (2017). "A Perspective on Crocus sativus L. (Saffron) Constituent Crocin: A Potent Water-Soluble Antioxidant and Potential Therapy for Alzheimer's Disease." Journal of Agricultural and Food Chemistry **65**(5): 1005-1020.

Fiori, J., M. Naldi, M. Bartolini and V. Andrisano (2012). "Disclosure of a fundamental clue for the elucidation of the myricetin mechanism of action as amyloid aggregation inhibitor by mass spectrometry." Electrophoresis **33**(22): 3380-3386.

Fremont, L. (2000). "Biological effects of resveratrol." Life Sci **66**(8): 663-673.

Frenkel, D., O. Katz and B. Solomon (2000). "Immunization against Alzheimer's beta -amyloid plaques via EFRH phage administration." Proc Natl Acad Sci U S A **97**(21): 11455-11459.

Ganesan, A. (2008). "The impact of natural products upon modern drug discovery." Curr Opin Chem Biol **12**(3): 306-317.

Garcia-Mediavilla, V., I. Crespo, P. S. Collado, A. Esteller, S. Sanchez-Campos, M. J. Tunon and J. Gonzalez-Gallego (2007). "The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells." Eur J Pharmacol **557**(2-3): 221-229.

Ghahghaei, A., S. Z. Bathaie and E. Bahraminejad (2012). "Mechanisms of the Effects of Crocin on Aggregation and Deposition of Aβ1–40 Fibrils in Alzheimer's Disease." International Journal of Peptide Research and Therapeutics **18**(4): 347-351.

Ghahghaei, A., S. Z. Bathaie, H. Kheirkhah and E. Bahraminejad (2013). "The protective effect of crocin on the amyloid fibril formation of Abeta42 peptide in vitro." Cell Mol Biol Lett **18**(3): 328-339.

Giraldo, E., A. Lloret, T. Fuchsberger and J. Viña (2014). "Aβ and tau toxicities in Alzheimer's are linked via oxidative stress-induced p38 activation: Protective role of vitamin E." Redox Biology **2**(1): 873-877.

Gnanapragasam, A., K. K. Ebenezar, V. Sathish, P. Govindaraju and T. Devaki (2004). "Protective effect of Centella asiatica on antioxidant tissue defense system against adriamycin induced cardiomyopathy in rats." Life Sci **76**(5): 585-597.

Goedert, M., A. Klug and R. A. Crowther (2006). "Tau protein, the paired helical filament and Alzheimer's disease." J Alzheimers Dis **9**(3 Suppl): 195-207.

Gong, Q. H., F. Li, F. Jin and J. S. Shia (2010). "Resveratrol attenuates neuroinflammation-mediated cognitive deficits in rats." Journal of Health Science **56**(6): 655-663.

Gotz, J., A. Schild, F. Hoerndli and L. Pennanen (2004). "Amyloid-induced neurofibrillary tangle formation in Alzheimer's disease: insight from transgenic mouse and tissue-culture models." Int J Dev Neurosci **22**(7): 453-465.

Granzotto, A. and P. Zatta (2011). "Resveratrol acts not through Anti-Aggregative pathways but mainly via its scavenging properties against Aβ and Aβ-metal complexes toxicity." PLoS ONE **6**(6).

Grimm, M. O., J. Kuchenbecker, S. Grosgen, V. K. Burg, B. Hundsdorfer, T. L. Rothhaar, P. Friess, M. C. de Wilde, L. M. Broersen, B. Penke, M. Peter, L. Vigh, H. S. Grimm and T. Hartmann (2011). "Docosahexaenoic acid reduces amyloid beta production via multiple pleiotropic mechanisms." J Biol Chem **286**(16): 14028-14039.

Grimm, M. O. W., J. Mett, C. P. Stahlmann, V. J. Haupenthal, T. Blümel, H. Stötzel, H. S. Grimm and T. Hartmann (2016). "Eicosapentaenoic acid and docosahexaenoic acid increase the degradation of amyloid-β by affecting insulin-degrading enzyme1." Biochemistry and Cell Biology **94**(6): 534-542.

Gu, X. H., L. J. Xu, Z. Q. Liu, B. Wei, Y. J. Yang, G. G. Xu, X. P. Yin and W. Wang (2016). "The flavonoid baicalein rescues synaptic plasticity and memory deficits in a mouse model of Alzheimer's disease." Behavioural Brain Research **311**: 309-321.

Gunasingh, M. J., J. E. Philip, B. S. Ashok, R. Kirubagaran, W. C. Jebaraj, G. D. Davis, S. Vignesh, S. Dhandayuthapani and R. Jayakumar (2008). "Melatonin prevents amyloid protofibrillar induced oxidative imbalance and biogenic amine catabolism." Life Sci **83**(3-4): 96-102.

Gupta, S., F. Afaq and H. Mukhtar (2001). "Selective growth-inhibitory, cell-cycle deregulatory and apoptotic response of apigenin in normal versus human prostate carcinoma cells." Biochemical and Biophysical Research Communications **287**(4): 914-920.

Gupta, Y. K., M. H. Veerendra Kumar and A. K. Srivastava (2003). "Effect of Centella asiatica on pentylenetetrazole-induced kindling, cognition and oxidative stress in rats." Pharmacol Biochem Behav **74**(3): 579-585.

Hadland, B. K., N. R. Manley, D. Su, G. D. Longmore, C. L. Moore, M. S. Wolfe, E. H. Schroeter and R. Kopan (2001). "Gamma -secretase inhibitors repress thymocyte development." Proc Natl Acad Sci U S A **98**(13): 7487-7491.

Hajipour, S., A. Sarkaki, Y. Farbood, A. Eidi, P. Mortazavi and Z. Valizadeh (2016). "Effect of gallic acid on dementia type of Alzheimer disease in rats: Electrophysiological and histological studies." Basic and Clinical Neuroscience **7**(2): 97-106.

Hardy, J. and D. Selkoe (2002). "The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics." Science's Compass **297**: 353-356.

Hartman, R. E., Y. Izumi, K. R. Bales, S. M. Paul, D. F. Wozniak and D. M. Holtzman (2005). "Treatment with an amyloid-beta antibody ameliorates plaque load, learning deficits, and hippocampal long-term potentiation in a mouse model of Alzheimer's disease." J Neurosci **25**(26): 6213-6220.

Harvey, A. L. (2008). "Natural products in drug discovery." Drug Discov Today **13**(19-20): 894-901.

Harvey, B. S., I. F. Musgrave, K. S. Ohlsson, A. Fransson and S. D. Smid (2011). "The green tea polyphenol (-)-epigallocatechin-3-gallate inhibits amyloid-β evoked fibril formation and neuronal cell death in vitro." Food Chemistry **129**(4): 1729-1736.

Hashimoto, M., S. Hossain, M. Katakura, A. Al Mamun and O. Shido (2015). "The binding of Aβ1-42 to lipid rafts of RBC is enhanced by dietary docosahexaenoic acid in rats: Implicates to Alzheimer's disease." Biochimica et Biophysica Acta - Biomembranes **1848**(6): 1402-1409.

Hashimoto, M., S. Hossain, T. Shimada, K. Sugioka, H. Yamasaki, Y. Fujii, Y. Ishibashi, J. Oka and O. Shido (2002). "Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats." J Neurochem **81**(5): 1084-1091.

Hashimoto, M., H. M. Shahdat, M. Katakura, Y. Tanabe, S. Gamoh, K. Miwa, T. Shimada and O. Shido (2009). "Effects of docosahexaenoic acid on in vitro amyloid beta peptide 25-35 fibrillation." Biochim Biophys Acta **1791**(4): 289-296.

Hashimoto, M., H. M. Shahdat, S. Yamashita, M. Katakura, Y. Tanabe, H. Fujiwara, S. Gamoh, T. Miyazawa, H. Arai, T. Shimada and O. Shido (2008). "Docosahexaenoic acid disrupts in vitro amyloid beta(1-40) fibrillation and concomitantly inhibits amyloid levels in cerebral cortex of Alzheimer's disease model rats." J Neurochem **107**(6): 1634-1646.

Hauber, I., H. Hohenberg, B. Holstermann, W. Hunstein and J. Hauber (2009). "The main green tea polyphenol epigallocatechin-3-gallate counteracts semen-mediated enhancement of HIV infection." Proc Natl Acad Sci U S A **106**(22): 9033-9038.

He, X., Z. Li, J. D. Rizak, S. Wu, Z. Wang, R. He, M. Su, D. Qin, J. Wang and X. Hu (2017). "Resveratrol attenuates formaldehyde induced hyperphosphorylation of tau protein and cytotoxicity in N2a cells." Frontiers in Neuroscience **10**(JAN).

Helmer, C., E. Peuchant, L. Letenneur, I. Bourdel-Marchasson, S. Larrieu, J. F. Dartigues, L. Dubourg, M. J. Thomas and P. Barberger-Gateau (2003). "Association between antioxidant nutritional indicators and the incidence of dementia: results from the PAQUID prospective cohort study." Eur J Clin Nutr **57**(12): 1555-1561.

Heo, H. J., D. O. Kim, S. J. Choi, D. H. Shin and C. Y. Lee (2004). "Potent Inhibitory effect of flavonoids in Scutellaria baicalensis on amyloid beta protein-induced neurotoxicity." J Agric Food Chem **52**(13): 4128-4132.

Heo, H. J. and C. Y. Lee (2004). "Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration." J Agric Food Chem **52**(25): 7514-7517.

Herrup, K. (2010). "Reimagining Alzheimer's disease--an age-based hypothesis." J Neurosci **30**(50): 16755-16762.

Hirohata, M., K. Hasegawa, S. Tsutsumi-Yasuhara, Y. Ohhashi, T. Ookoshi, K. Ono, M. Yamada and H. Naiki (2007). "The anti-amyloidogenic effect is exerted against Alzheimer's beta-amyloid fibrils in vitro by preferential and reversible binding of flavonoids to the amyloid fibril structure." Biochemistry **46**(7): 1888-1899.

Ho, J. H. and Y. L. Chang (2004). "Protective effects of quercetin and vitamin C against oxidative stress-induced neurodegeneration." Journal of Agricultural and Food Chemistry **52**(25): 7514-7517.

Hossain, S., M. Hashimoto, M. Katakura, K. Miwa, T. Shimada and O. Shido (2009). "Mechanism of docosahexaenoic acid-induced inhibition of in vitro Aβ1-42 fibrillation and Aβ1-42-induced toxicity in SH-S5Y5 cells." Journal of Neurochemistry **111**(2): 568-579.

Huang, H. C., P. Chang, X. L. Dai and Z. F. Jiang (2012). "Protective effects of curcumin on amyloid-b-induced neuronal oxidative damage." Neurochemical Research **37**(7): 1584-1597.

Huang, H. C., B. W. Zheng, Y. Guo, J. Zhao, J. Y. Zhao, X. W. Ma and Z. F. Jiang (2016). "Antioxidative and Neuroprotective Effects of Curcumin in an Alzheimer's Disease Rat Model Co-Treated with Intracerebroventricular Streptozotocin and Subcutaneous D-Galactose." Journal of Alzheimer's Disease **52**(3): 899-911.

Huang, M., X. Jiang, Y. Liang, Q. Liu, S. Chen and Y. Guo (2017). "Berberine improves cognitive impairment by promoting autophagic clearance and inhibiting production of β-amyloid in APP/tau/PS1 mouse model of Alzheimer's disease." Experimental Gerontology **91**: 25-33.

Huang, Y. S. and J. T. Zhang (1992). "[Antioxidative effect of three water-soluble components isolated from Salvia miltiorrhiza in vitro]." Yao Xue Xue Bao **27**(2): 96-100.

Jang, J. H. and Y. J. Surh (2003). "Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death." Free Radic Biol Med **34**(8): 1100-1110.

Jayamani, J. and G. Shanmugam (2014). "Gallic acid, one of the components in many plant tissues, is a potential inhibitor for insulin amyloid fibril formation." European Journal of Medicinal Chemistry **85**: 352-358.

Jeon, S. Y., K. Bae, Y. H. Seong and K. S. Song (2003). "Green tea catechins as a BACE1 (beta-secretase) inhibitor." Bioorg Med Chem Lett **13**(22): 3905-3908.

Jeong, J. H., H. J. Kim, T. J. Lee, M. K. Kim, E. S. Park and B. S. Choi (2004). "Epigallocatechin 3-gallate attenuates neuronal damage induced by 3-hydroxykynurenine." Toxicology **195**(1): 53-60.

Jesudason, E. P., B. Baben, B. S. Ashok, J. G. Masilamoni, R. Kirubagaran, W. C. Jebaraj and R. Jayakumar (2007). "Anti-inflammatory effect of melatonin on A beta vaccination in mice." Mol Cell Biochem **298**(1-2): 69-81.

Ji, H. F. and L. Shen (2011). "Berberine: a potential multipotent natural product to combat Alzheimer's disease." Molecules **16**(8): 6732-6740.

Jia, L., J. Liu, Z. Song, X. Pan, L. Chen, X. Cui and M. Wang (2012). "Berberine suppresses amyloid-beta-induced inflammatory response in microglia by inhibiting nuclear factor-kappaB and mitogen-activated protein kinase signalling pathways." Journal of Pharmacy and Pharmacology **64**(10): 1510-1521.

Jiang, B., J. H. Liu, Y. M. Bao and L. J. An (2003). "Hydrogen peroxide-induced apoptosis in pc12 cells and the protective effect of puerarin." Cell Biol Int **27**(12): 1025-1031.

Jimenez-Aliaga, K., P. Bermejo-Bescos, J. Benedi and S. Martin-Aragon (2011). "Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells." Life Sci **89**(25-26): 939-945.

Jin, B. H., L. B. Qian, S. A. Chen, J. Li, H. P. Wang, I. C. Bruce, J. Lin and Q. Xia (2009). "Apigenin protects endothelium-dependent relaxation of rat aorta against oxidative stress." European Journal of Pharmacology **616**(1-3): 200-205.

Johansson, A. S., A. Garlind, F. Berglind-Dehlin, G. Karlsson, K. Edwards, P. Gellerfors, F. Ekholm-Pettersson, J. Palmblad and L. Lannfelt (2007). "Docosahexaenoic acid stabilizes soluble amyloid-beta protofibrils and sustains amyloid-beta-induced neurotoxicity in vitro." FEBS J **274**(4): 990-1000.

Kanski, J., M. Aksenova, A. Stoyanova and D. A. Butterfield (2002). "Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture systems in vitro: structure-activity studies." J Nutr Biochem **13**(5): 273-281.

Kanski, J., M. Aksenova, A. Stoyanova and D. A. Butterfield (2002). "Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture systems in vitro: Structure-activity studies." Journal of Nutritional Biochemistry **13**(5): 273-281.

Kapoor, A., B. J. Wang, W. M. Hsu, M. Y. Chang, S. M. Liang and Y. F. Liao (2013). "Retinoic acid-elicited RARalpha/RXRalpha signaling attenuates Abeta production by directly inhibiting gamma-secretase-mediated cleavage of amyloid precursor protein." ACS Chem Neurosci **4**(7): 1093-1100.

Karuppagounder, S. S., J. T. Pinto, H. Xu, H. L. Chen, M. F. Beal and G. E. Gibson (2009). "Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease." Neurochemistry International **54**(2): 111-118.

Kim, C. Y., C. Lee, G. H. Park and J. H. Jang (2009). "Neuroprotective effect of epigallocatechin-3-gallate against β-amyloid-induced oxidative and nitrosative cell death via augmentation of antioxidant defense capacity." Archives of Pharmacal Research **32**(6): 869-881.

Kim, M. J., A. R. Seong, J. Y. Yoo, C. H. Jin, Y. H. Lee, Y. J. Kim, J. Lee, W. J. Jun and H. G. Yoon (2011). "Gallic acid, a histone acetyltransferase inhibitor, suppresses beta-amyloid neurotoxicity by inhibiting microglial-mediated neuroinflammation." Mol Nutr Food Res **55**(12): 1798-1808.

Kim, S., K. J. Choi, S. J. Cho, S. M. Yun, J. P. Jeon, Y. H. Koh, J. Song, G. V. W. Johnson and C. Jo (2016). "Fisetin stimulates autophagic degradation of phosphorylated tau via the activation of TFEB and Nrf2 transcription factors." Scientific Reports **6**.

Kirkitadze, M. D., M. M. Condron and D. B. Teplow (2001). "Identification and characterization of key kinetic intermediates in amyloid beta-protein fibrillogenesis." J Mol Biol **312**(5): 1103-1119.

Klafki, H. W., M. Staufenbiel, J. Kornhuber and J. Wiltfang (2006). "Therapeutic approaches to Alzheimer's disease." Brain **129**(Pt 11): 2840-2855.

Klyubin, I., D. M. Walsh, C. A. Lemere, W. K. Cullen, G. M. Shankar, V. Betts, E. T. Spooner, L. Jiang, R. Anwyl, D. J. Selkoe and M. J. Rowan (2005). "Amyloid beta protein immunotherapy neutralizes Abeta oligomers that disrupt synaptic plasticity in vivo." Nat Med **11**(5): 556-561.

Kong, Y. K., L. C. Yao, C. Z. Lu, Y. Sun and J. Ni (2007). "[Effects of vitamin E on expression of PS-1 and production of Abeta in the hippocampus of female senile rats]." Zhongguo Ying Yong Sheng Li Xue Za Zhi **23**(2): 237-240.

Kook, S. Y., K. M. Lee, Y. Kim, M. Y. Cha, S. Kang, S. H. Baik, H. Lee, R. Park and I. Mook-Jung (2014). "High-dose of vitamin C supplementation reduces amyloid plaque burden and ameliorates pathological changes in the brain of 5XFAD mice." Cell Death Dis **5**: e1083.

Koryakina, A., J. Aeberhard, S. Kiefer, M. Hamburger and P. Kuenzi (2009). "Regulation of secretases by all-trans-retinoic acid." FEBS J **276**(9): 2645-2655.

Kumar, A., P. S. Naidu, N. Seghal and S. S. V. Padi (2007). "Neuroprotective effects of resveratrol against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress in rats." Pharmacology **79**(1): 17-26.

Kumar, A., A. Singh and Ekavali (2015). "A review on Alzheimer's disease pathophysiology and its management: an update." Pharmacological Reports **67**(2): 195-203.

Kurz, A. and R. Perneczky (2011). "Amyloid clearance as a treatment target against Alzheimer's disease." J Alzheimers Dis **24 Suppl 2**: 61-73.

Ladiwala, A. R. A., J. C. Lin, S. S. Bale, A. M. Marcelino-Cruz, M. Bhattacharya, J. S. Dordick and P. M. Tessier (2010). "Resveratrol selectively remodels soluble oligomers and fibrils of amyloid Aβ into off-pathway conformers." Journal of Biological Chemistry **285**(31): 24228-24237.

LaFerla, F. M. and S. Oddo (2005). "Alzheimer's disease: Abeta, tau and synaptic dysfunction." Trends Mol Med **11**(4): 170-176.

Lahiri, D. K., T. Utsuki, D. Chen, M. R. Farlow, M. Shoaib, D. K. Ingram and N. H. Greig (2002). Nicotine reduces the secretion of Alzheimer's β-amyloid precursor protein containing β-amyloid peptide in the rat without altering synaptic proteins. Annals of the New York Academy of Sciences. **965:** 364-372.

Lahlou, M. (2007). "Screening of natural products for drug discovery." Expert Opin Drug Discov **2**(5): 697-705.

Laurent, C., S. Eddarkaoui, M. Derisbourg, A. Leboucher, D. Demeyer, S. Carrier, M. Schneider, M. Hamdane, C. E. Muller, L. Buee and D. Blum (2014). "Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology." Neurobiol Aging **35**(9): 2079-2090.

Lee, J. W., Y. K. Lee, J. O. Ban, T. Y. Ha, Y. P. Yun, S. B. Han, K. W. Oh and J. T. Hong (2009). "Green tea (-)-epigallocatechin-3-gallate inhibits beta-amyloid-induced cognitive dysfunction through modification of secretase activity via inhibition of ERK and NF-kappaB pathways in mice." J Nutr **139**(10): 1987-1993.

Lee, V. M., M. Goedert and J. Q. Trojanowski (2001). "Neurodegenerative tauopathies." Annu Rev Neurosci **24**: 1121-1159.

Lee, V. M. and J. Q. Trojanowski (2006). "Progress from Alzheimer's tangles to pathological tau points towards more effective therapies now." J Alzheimers Dis **9**(3 Suppl): 257-262.

Lee, Y. J., D. Y. Choi, Y. P. Yun, S. B. Han, K. W. Oh and J. T. Hong (2013). "Epigallocatechin-3-gallate prevents systemic inflammation-induced memory

deficiency and amyloidogenesis via its anti-neuroinflammatory properties." J Nutr Biochem **24**(1): 298-310.

Lee, Y. K., D. Y. Yuk, J. W. Lee, S. Y. Lee, T. Y. Ha, K. W. Oh, Y. P. Yun and J. T. Hong (2009). "(-)-Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of beta-amyloid generation and memory deficiency." Brain Research **1250**: 164-174.

Li, Q., D. Wu, L. Zhang and Y. Zhang (2010). "Effects of galantamine on B-amyloid release and beta-site cleaving enzyme 1 expression in differentiated human neuroblastoma SH-SY5Y cells." Experimental Gerontology **45**(11): 842-847.

Lim, G. P., F. Calon, T. Morihara, F. Yang, B. Teter, O. Ubeda, N. Salem, Jr., S. A. Frautschy and G. M. Cole (2005). "A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model." J Neurosci **25**(12): 3032-3040.

Lim, G. P., T. Chu, F. Yang, W. Beech, S. A. Frautschy and G. M. Cole (2001). "The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse." J Neurosci **21**(21): 8370-8377.

Lin, C. F., K. H. Yu, C. P. Jheng, R. Chung and C. I. Lee (2013). "Curcumin reduces amyloid fibrillation of prion protein and decreases reactive oxidative stress." Pathogens **2**(3): 506-519.

Lin, R., X. Chen, W. Li, Y. Han, P. Liu and R. Pi (2008). "Exposure to metal ions regulates mRNA levels of APP and BACE1 in PC12 cells: blockage by curcumin." Neurosci Lett **440**(3): 344-347.

Linert, W., M. H. Bridge, M. Huber, K. B. Bjugstad, S. Grossman and G. W. Arendash (1999). "In vitro and in vivo studies investigating possible antioxidant actions of nicotine: relevance to Parkinson's and Alzheimer's diseases." Biochim Biophys Acta **1454**(2): 143-152.

Liu, Y., T. L. Pukala, I. F. Musgrave, D. M. Williams, F. C. Dehle and J. A. Carver (2013). "Gallic acid is the major component of grape seed extract that inhibits amyloid fibril formation." Bioorg Med Chem Lett **23**(23): 6336-6340.

Lombardo, J. A., E. A. Stern, M. E. McLellan, S. T. Kajdasz, G. A. Hickey, B. J. Bacskai and B. T. Hyman (2003). "Amyloid-beta antibody treatment leads to rapid normalization of plaque-induced neuritic alterations." J Neurosci **23**(34): 10879-10883.

Loureiro, J., S. Andrade, A. Duarte, A. Neves, J. Queiroz, C. Nunes, E. Sevin, L. Fenart, F. Gosselet, M. Coelho and M. Pereira (2017). "Resveratrol and Grape Extract-loaded Solid Lipid Nanoparticles for the Treatment of Alzheimer's Disease." Molecules **22**(2): 277.

Lu, J. H., M. T. Ardah, S. S. Durairajan, L. F. Liu, L. X. Xie, W. F. Fong, M. Y. Hasan, J. D. Huang, O. M. El-Agnaf and M. Li (2011). "Baicalein inhibits formation of alpha-synuclein oligomers within living cells and prevents Abeta peptide fibrillation and oligomerisation." Chembiochem **12**(4): 615-624.

Lu, X., L. Ma, L. Ruan, Y. Kong, H. Mou, Z. Zhang, Z. Wang, J. M. Wang and Y. Le (2010). "Resveratrol differentially modulates inflammatory responses of microglia and astrocytes." J Neuroinflammation **7**: 46.

Luo, Y., B. Bolon, S. Kahn, B. D. Bennett, S. Babu-Khan, P. Denis, W. Fan, H. Kha, J. Zhang, Y. Gong, L. Martin, J. C. Louis, Q. Yan, W. G. Richards, M. Citron and R. Vassar (2001). "Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation." Nat Neurosci **4**(3): 231-232.

Ma, X. R., Z. K. Sun, Y. R. Liu, Y. J. Jia, B. A. Zhang and J. W. Zhang (2013). "Resveratrol improves cognition and reduces oxidative stress in rats with vascular dementia." Neural Regeneration Research **8**(22): 2050-2059.

Mahdy, H. M., M. R. Mohamed, M. A. Emam, A. M. Karim, A. B. Abdel-Naim and A. E. Khalifa (2014). "The anti-apoptotic and anti-inflammatory properties of puerarin attenuate 3-nitropropionic-acid induced neurotoxicity in rats." Can J Physiol Pharmacol **92**(3): 252-258.

Maher, P. (2009). "Modulation of multiple pathways involved in the maintenance of neuronal function during aging by fisetin." Genes Nutr **4**(4): 297-307.

Maia, L. and A. de Mendonca (2002). "Does caffeine intake protect from Alzheimer's disease?" Eur J Neurol **9**(4): 377-382.

Mansouri, M. T., Y. Farbood, M. J. Sameri, A. Sarkaki, B. Naghizadeh and M. Rafeirad (2013). "Neuroprotective effects of oral gallic acid against oxidative stress induced by 6-hydroxydopamine in rats." Food Chem **138**(2-3): 1028-1033.

Mansouri, M. T., B. Naghizadeh, B. Ghorbanzadeh, Y. Farbood, A. Sarkaki and K. Bavarsad (2013). "Gallic acid prevents memory deficits and oxidative stress induced by intracerebroventricular injection of streptozotocin in rats." Pharmacology Biochemistry and Behavior **111**: 90-96.

Marambaud, P., H. Zhao and P. Davies (2005). "Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides." J Biol Chem **280**(45): 37377-37382.

Marfak, A., P. Trouillas, D. P. Allais, C. A. Calliste, J. Cook-Moreau and J. L. Duroux (2003). "Mechanisms of transformation of the antioxidant kaempferol into depsides. Gamma-radiolysis study in methanol and ethanol." Radiat Res **160**(3): 355-365.

Martin, A. (2003). "Antioxidant vitamins E and C and risk of Alzheimer's disease." Nutr Rev **61**(2): 69-73.

Maruf, A. A., H. Lip, H. Wong and P. J. O'Brien (2015). "Protective effects of ferulic acid and related polyphenols against glyoxal- or methylglyoxal-induced cytotoxicity and oxidative stress in isolated rat hepatocytes." Chemico-Biological Interactions **234**: 96-104.

Matharu, B., G. Gibson, R. Parsons, T. N. Huckerby, S. A. Moore, L. J. Cooper, R. Millichamp, D. Allsop and B. Austen (2009). "Galantamine inhibits β-amyloid aggregation and cytotoxicity." Journal of the Neurological Sciences **280**(1-2): 49-58.

Matsubara, E., T. Bryant-Thomas, J. P. Quinto, T. L. Henry, B. Poeggeler, D. Herbert, F. Cruz-Sanchez, Y. J. Chyan, M. A. Smith, G. Perry, M. Shoji, K. Abe, A. Leone, I.

Grundke-Ikbal, G. L. Wilson, J. Ghiso, C. Williams, L. M. Refolo and M. A. Pappolla (2003). "Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer's disease." Journal of Neurochemistry **85**(5): 1101-1108.

Mawuenyega, K. G., W. Sigurdson, V. Ovod, L. Munsell, T. Kasten, J. C. Morris, K. E. Yarasheski and R. J. Bateman (2010). "Decreased clearance of CNS beta-amyloid in Alzheimer's disease." Science **330**(6012): 1774.

McClure, R., H. Ong, V. Janve, S. Barton, M. Zhu, B. Li, M. Dawes, W. G. Jerome, A. Anderson, P. Massion, J. C. Gore and W. Pham (2017). "Aerosol Delivery of Curcumin Reduced Amyloid-β Deposition and Improved Cognitive Performance in a Transgenic Model of Alzheimer's Disease." Journal of Alzheimer's Disease **55**(2): 797-811.

McKay, D. L. and J. B. Blumberg (2006). "A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.)." Phytotherapy Research **20**(7): 519-530.

Mei, Z. R., X. P. Tan, S. Z. Liu and H. H. Huang (2016). "Puerarin alleviates cognitive impairment and tau hyperphosphorylation in APP/PS1 transgenic mice." Zhongguo Zhongyao Zazhi **41**(17): 3285-3289.

Melo, J. B., C. Sousa, P. Garção, C. R. Oliveira and P. Agostinho (2009). "Galantamine protects against oxidative stress induced by amyloid-beta peptide in cortical neurons." European Journal of Neuroscience **29**(3): 455-464.

Meraz-Ríos, M., K. León, V. Campos-Penã, M. Anda-Hernández and R. Mena-López (2010). "Tau oligomers and aggregation in Alzheimer's disease." Journal of Neurochemistry **112**: 1353–1367.

Mori, T., N. Koyama, M. V. Guillot-Sestier, J. Tan and T. Town (2013). "Ferulic acid is a nutraceutical beta-secretase modulator that improves behavioral impairment and alzheimer-like pathology in transgenic mice." PLoS One **8**(2): e55774.

Moslehi, M., A. Meshkini and R. Yazdanparast (2012). "Flavonoid baicalein modulates H2O2-induced mitogen-activated protein kinases activation and cell death in SK-N-MC cells." Cellular and Molecular Neurobiology **32**(4): 549-560.

Moussa, C., M. Hebron, X. Huang, J. Ahn, R. A. Rissman, P. S. Aisen and R. S. Turner (2017). "Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease." Journal of Neuroinflammation **14**(1).

Murakami, K., N. Murata, Y. Ozawa, N. Kinoshita, K. Irie, T. Shirasawa and T. Shimizu (2011). "Vitamin C restores behavioral deficits and amyloid-beta oligomerization without affecting plaque formation in a mouse model of Alzheimer's disease." J Alzheimers Dis **26**(1): 7-18.

Naghizadeh, B., M. T. Mansouri, B. Ghorbanzadeh, Y. Farbood and A. Sarkaki (2013). "Protective effects of oral crocin against intracerebroventricular streptozotocin-induced spatial memory deficit and oxidative stress in rats." Phytomedicine **20**(6): 537-542.

Nagy, Z., K. A. Jobst, M. M. Esiri, J. H. Morris, E. M. King, B. MacDonald, S. Litchfield, L. Barnetson and A. D. Smith (1996). "Hippocampal pathology reflects memory deficit and brain imaging measurements in Alzheimer's disease: clinicopathologic correlations using three sets of pathologic diagnostic criteria." Dementia **7**(2): 76-81.

Nam, K. N., Y. M. Park, H. J. Jung, J. Y. Lee, B. D. Min, S. U. Park, W. S. Jung, K. H. Cho, J. H. Park, I. Kang, J. W. Hong and E. H. Lee (2010). "Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells." Eur J Pharmacol **648**(1-3): 110-116.

Nehlig, A. (1999). "Are we dependent upon coffee and caffeine? A review on human and animal data." Neurosci Biobehav Rev **23**(4): 563-576.

Nie, H. Z., Z. Q. Li, Q. X. Yan, Z. J. Wang, W. J. Zhao, L. C. Guo and M. Yin (2011). "Nicotine decreases beta-amyloid through regulating BACE1 transcription in SH-EP1-alpha4beta2 nAChR-APP695 cells." Neurochem Res **36**(5): 904-912.

Nordberg, A., E. Hellstrom-Lindahl, M. Lee, M. Johnson, M. Mousavi, R. Hall, E. Perry, I. Bednar and J. Court (2002). "Chronic nicotine treatment reduces beta-amyloidosis in the brain of a mouse model of Alzheimer's disease (APPsw)." J Neurochem **81**(3): 655-658.

Oddo, S., L. Billings, J. P. Kesslak, D. H. Cribbs and F. M. LaFerla (2004). "Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome." Neuron **43**(3): 321-332.

Ono, K., K. Hasegawa, H. Naiki and M. Yamada (2004). "Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro." J Neurosci Res **75**(6): 742-750.

Ono, K., K. Hasegawa, M. Yamada and H. Naiki (2002). "Nicotine breaks down preformed Alzheimer's beta-amyloid fibrils in vitro." Biol Psychiatry **52**(9): 880-886.

Ono, K., M. Hirohata and M. Yamada (2005). "Ferulic acid destabilizes preformed beta-amyloid fibrils in vitro." Biochem Biophys Res Commun **336**(2): 444-449.

Ono, K., Y. Yoshiike, A. Takashima, K. Hasegawa, H. Naiki and M. Yamada (2003). "Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: implications for the prevention and therapeutics of Alzheimer's disease." J Neurochem **87**(1): 172-181.

Ono, K., Y. Yoshiike, A. Takashima, K. Hasegawa, H. Naiki and M. Yamada (2004). "Vitamin A exhibits potent antiamyloidogenic and fibril-destabilizing effects in vitro." Experimental Neurology **189**(2): 380-392.

Panahi, N., M. Mahmoudian, P. Mortazavi and G. S. Hashjin (2013). "Effects of berberine on β-secretase activity in a rabbit model of Alzheimer's disease." Archives of Medical Science **9**(1): 146-150.

Panes, J., M. E. Gerritsen, D. C. Anderson and D. N. Granger (1996). "Apigenin inhibits TNF-induced ICAM-1 upregulation in splanchnic organs." Gastroenterology **110**(4): A986-A986.

Panmanee, J., C. Nopparat, N. Chavanich, M. Shukla, S. Mukda, W. Song, B. Vincent and P. Govitrapong (2015). "Melatonin regulates the transcription of betaAPP-cleaving secretases mediated through melatonin receptors in human neuroblastoma SH-SY5Y cells." J Pineal Res **59**(3): 308-320.

Papandreou, M. A., C. D. Kanakis, M. G. Polissiou, S. Efthimiopoulos, P. Cordopatis, M. Margarity and F. N. Lamari (2006). "Inhibitory activity on amyloid-beta aggregation and antioxidant properties of Crocus sativus stigmas extract and its crocin constituents." J Agric Food Chem **54**(23): 8762-8768.

Pappolla, M., P. Bozner, C. Soto, H. Shao, N. K. Robakis, M. Zagorski, B. Frangione and J. Ghiso (1998). "Inhibition of Alzheimer beta-fibrillogenesis by melatonin." J Biol Chem **273**(13): 7185-7188.

Pappolla, M. A., Y. J. Chyan, B. Poeggeler, B. Frangione, G. Wilson, J. Ghiso and R. J. Reiter (2000). "An assessment of the antioxidant and the antiamyloidogenic properties of melatonin: Implications for Alzheimer's disease." Journal of Neural Transmission **107**(2): 203-231.

Park, S. Y., H. S. Kim, E. K. Cho, B. Y. Kwon, S. Phark, K. W. Hwang and D. Sul (2008). "Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation." Food Chem Toxicol **46**(8): 2881-2887.

Patil, S. P., S. Maki, S. A. Khedkar, A. C. Rigby and C. Chan (2010). "Withanolide A and Asiatic Acid Modulate Multiple Targets Associated with Amyloid-beta Precursor Protein Processing and Amyloid-beta Protein Clearance." Journal of Natural Products **73**(7): 1196-1202.

Pavlica, S. and R. Gebhardt (2010). "Protective effects of flavonoids and two metabolites against oxidative stress in neuronal PC12 cells." Life Sci **86**(3-4): 79-86.

Peng, Y., L. Jiang, D. Y. Lee, S. C. Schachter, Z. Ma and C. A. Lemere (2006). "Effects of huperzine A on amyloid precursor protein processing and beta-amyloid generation in human embryonic kidney 293 APP Swedish mutant cells." J Neurosci Res **84**(4): 903-911.

Peng, Y., D. Y. W. Lee, L. Jiang, Z. Ma, S. C. Schachter and C. A. Lemere (2007). "Huperzine A regulates amyloid precursor protein processing via protein kinase C and mitogen-activated protein kinase pathways in neuroblastoma SK-N-SH cells over-expressing wild type human amyloid precursor protein 695." Neuroscience **150**(2): 386-395.

Pickhardt, M., Z. Gazova, M. von Bergen, I. Khlistunova, Y. Wang, A. Hascher, E. M. Mandelkow, J. Biernat and E. Mandelkow (2005). "Anthraquinones inhibit tau aggregation and dissolve Alzheimer's paired helical filaments in vitro and in cells." J Biol Chem **280**(5): 3628-3635.

Picone, P., D. Nuzzo and M. Di Carlo (2013). "Ferulic acid: A natural antioxidant against oxidative stress induced by oligomeric A-beta on sea urchin embryo." Biological Bulletin **224**(1): 18-28.

Poeggeler, B., L. Miravalle, M. G. Zagorski, T. Wisniewski, Y. J. Chyan, Y. Zhang, H. Shao, T. Bryant-Thomas, R. Vidal, B. Frangione, J. Ghiso and M. A. Pappolla (2001). "Melatonin reverses the profibrillogenic activity of apolipoprotein E4 on the alzheimer amyloid Aβ peptidet." Biochemistry **40**(49): 14995-15001.

Popik, P., B. Bobula, M. Janusz, J. Lisowski and J. Vetulani (1999). "Colostrinin, a polypeptide isolated from early milk, facilitates learning and memory in rats." Pharmacol Biochem Behav **64**(1): 183-189.

Prasanthi, J. R., B. Dasari, G. Marwarha, T. Larson, X. Chen, J. D. Geiger and O. Ghribi (2010). "Caffeine protects against oxidative stress and Alzheimer's disease-like pathology in rabbit hippocampus induced by cholesterol-enriched diet." Free Radic Biol Med **49**(7): 1212-1220.

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

Qosa, H., A. H. Abuznait, R. A. Hill and A. Kaddoumi (2012). "Enhanced brain amyloid-beta clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease." J Alzheimers Dis **31**(1): 151-165.

Rackova, L., M. Majekova, D. Kost'alova and M. Stefek (2004). "Antiradical and antioxidant activities of alkaloids isolated from Mahonia aquifolium. Structural aspects." Bioorg Med Chem **12**(17): 4709-4715.

Rao, P. P. N., T. Mohamed and W. Osman (2013). "Investigating the binding interactions of galantamine with β-amyloid peptide." Bioorganic and Medicinal Chemistry Letters **23**(1): 239-243.

Ray, B. and D. K. Lahiri (2009). "Neuroinflammation in Alzheimer's disease: different molecular targets and potential therapeutic agents including curcumin." Current Opinion in Pharmacology **9**(4): 434-444.

Rege, S. D., T. Geetha, T. L. Broderick and J. R. Babu (2015). "Resveratrol protects β amyloid-induced oxidative damage and memory associated proteins in H19-7 hippocampal neuronal cells." Current Alzheimer Research **12**(2): 147-156.

Regitz, C., L. M. Dussling and U. Wenzel (2014). "Amyloid-beta (Abeta(1)(-)(4)(2))-induced paralysis in Caenorhabditis elegans is inhibited by the polyphenol quercetin through activation of protein degradation pathways." Mol Nutr Food Res **58**(10): 1931-1940.

Rezai-Zadeh, K., G. W. Arendash, H. Hou, F. Fernandez, M. Jensen, M. Runfeldt, R. D. Shytle and J. Tan (2008). "Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice." Brain Res **1214**: 177-187.

Rezai-Zadeh, K., D. Shytle, N. Sun, T. Mori, H. Hou, D. Jeanniton, J. Ehrhart, K. Townsend, J. Zeng, D. Morgan, J. Hardy, T. Town and J. Tan (2005). "Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice." Journal of Neuroscience **25**(38): 8807-8814.

Rezai-Zadeh, K., D. Shytle, N. Sun, T. Mori, H. Hou, D. Jeanniton, J. Ehrhart, K. Townsend, J. Zeng, D. Morgan, J. Hardy, T. Town and J. Tan (2005). "Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice." J Neurosci **25**(38): 8807-8814.

Rosales-Corral, S., D. X. Tan, R. J. Reiter, M. Valdivia-Velazquez, G. Martinez-Barboza, J. P. Acosta-Martinez and G. G. Ortiz (2003). "Orally administered melatonin reduces oxidative stress and proinflammatory cytokines induced by amyloid-beta peptide in rat brain: a comparative, in vivo study versus vitamin C and E." J Pineal Res **35**(2): 80-84.

Rudnitskaya, E. A., N. A. Muraleva, K. Y. Maksimova, E. Kiseleva, N. G. Kolosova and N. A. Stefanova (2015). "Melatonin Attenuates Memory Impairment, Amyloid-beta Accumulation, and Neurodegeneration in a Rat Model of Sporadic Alzheimer's Disease." J Alzheimers Dis **47**(1): 103-116.

Ruiz-Medina, J., A. Pinto-Xavier, M. Rodríguez-Arias, J. Miñarro and O. Valverde (2013). "Influence of chronic caffeine on MDMA-induced behavioral and neuroinflammatory response in mice." Psychopharmacology **226**(2): 433-444.

Sagare, A. P., R. D. Bell and B. V. Zlokovic (2012). "Neurovascular dysfunction and faulty amyloid beta-peptide clearance in Alzheimer disease." Cold Spring Harb Perspect Med **2**(10).

Sahlin, C., F. E. Pettersson, L. N. Nilsson, L. Lannfelt and A. S. Johansson (2007). "Docosahexaenoic acid stimulates non-amyloidogenic APP processing resulting in reduced Abeta levels in cellular models of Alzheimer's disease." Eur J Neurosci **26**(4): 882-889.

Salomon, A. R., K. J. Marcinowski, R. P. Friedland and M. G. Zagorski (1996). "Nicotine inhibits amyloid formation by the beta-peptide." Biochemistry **35**(42): 13568-13578.

Scarpini, E., P. Scheltens and H. Feldman (2003). "Treatment of Alzheimer's disease: current status and new perspectives." Lancet Neurol **2**(9): 539-547.

Schenk, D., R. Barbour, W. Dunn, G. Gordon, H. Grajeda, T. Guido, K. Hu, J. Huang, K. Johnson-Wood, K. Khan, D. Kholodenko, M. Lee, Z. Liao, I. Lieberburg, R. Motter, L. Mutter, F. Soriano, G. Shopp, N. Vasquez, C. Vandevert, S. Walker, M. Wogulis, T. Yednock, D. Games and P. Seubert (1999). "Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse." Nature **400**(6740): 173-177.

Schneider, A. and E. Mandelkow (2008). "Tau-based treatment strategies in neurodegenerative diseases." Neurotherapeutics **5**(3): 443-457.

Schott, J. M. and T. Revesz (2013). "Inflammation in Alzheimer's disease: insights from immunotherapy." Brain **136**(Pt 9): 2654-2656.

Schuster, D., A. Rajendran, S. W. Hui, T. Nicotera, T. Srikrishnan and M. L. Kruzel (2005). "Protective effect of colostrinin on neuroblastoma cell survival is due to reduced aggregation of beta-amyloid." Neuropeptides **39**(4): 419-426.

Shankar, G. M., S. Li, T. H. Mehta, A. Garcia-Munoz, N. E. Shepardson, I. Smith, F. M. Brett, M. A. Farrell, M. J. Rowan, C. A. Lemere, C. M. Regan, D. M. Walsh, B. L. Sabatini and D. J. Selkoe (2008). "Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory." Nat Med **14**(8): 837-842.

Sharma, B., S. Kalita, A. Paul, B. Mandal and S. Paul (2016). "The role of caffeine as an inhibitor in the aggregation of amyloid forming peptides: A unified molecular dynamics simulation and experimental study." RSC Advances **6**(82): 78548-78558.

Shen, Y., H. Zhang, L. Wang, H. Qian, Y. Qi, X. Miao, L. Cheng and X. Qi (2016). "Protective effect of ferulic acid against 2,2'-azobis(2-amidinopropane) dihydrochloride-induced oxidative stress in PC12 cells." Cellular and Molecular Biology **62**(1): 109-116.

Shi, X., Z. Zheng, J. Li, Z. Xiao, W. Qi, A. Zhang, Q. Wu and Y. Fang (2015). "Curcumin inhibits Aβ-induced microglial inflammatory responses in vitro: Involvement of ERK1/2 and p38 signaling pathways." Neuroscience Letters **594**: 105-110.

Shimmyo, Y., T. Kihara, A. Akaike, T. Niidome and H. Sugimoto (2008). "Epigallocatechin-3 -gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation." NeuroReport **19**(13): 1329-1333.

Shimmyo, Y., T. Kihara, A. Akaike, T. Niidome and H. Sugimoto (2008). "Flavonols and flavones as BACE-1 inhibitors: structure-activity relationship in cell-free, cell-based and in silico studies reveal novel pharmacophore features." Biochim Biophys Acta **1780**(5): 819-825.

Shimmyo, Y., T. Kihara, A. Akaike, T. Niidome and H. Sugimoto (2008). "Multifunction of myricetin on A beta: neuroprotection via a conformational change of A beta and reduction of A beta via the interference of secretases." J Neurosci Res **86**(2): 368-377.

Shinomol, G. K. and Muralidhara (2008). "Effect of Centella asiatica leaf powder on oxidative markers in brain regions of prepubertal mice in vivo and its in vitro efficacy to ameliorate 3-NPA-induced oxidative stress in mitochondria." Phytomedicine **15**(11): 971-984.

Shukla, S. and S. Gupta (2010). "Apigenin: A Promising Molecule for Cancer Prevention." Pharmaceutical Research **27**(6): 962-978.

Sil, S., T. Ghosh, P. Gupta, R. Ghosh, S. N. Kabir and A. Roy (2016). "Dual Role of Vitamin C on the Neuroinflammation Mediated Neurodegeneration and Memory Impairments in Colchicine Induced Rat Model of Alzheimer Disease." Journal of Molecular Neuroscience **60**(4): 421-435.

Small, S. and K. Duff (2008). "Linking Ab and Tau in Late-Onset Alzheimer's Disease: A Dual Pathway Hypothesis." Neuron: 534-542.

Soliman, M. L., J. D. Geiger and X. Chen (2017). "Caffeine Blocks HIV-1 Tat-Induced Amyloid Beta Production and Tau Phosphorylation." Journal of Neuroimmune Pharmacology **12**(1): 163-170.

Solomon, B., R. Koppel, D. Frankel and E. Hanan-Aharon (1997). "Disaggregation of Alzheimer beta-amyloid by site-directed mAb." Proc Natl Acad Sci U S A **94**(8): 4109-4112.

Song, S. M., Y. X. Wang, L. M. Xiong, L. B. Qu and M. T. Xu (2012). "AFM and fluorescence spectrascopy investigation for disaggregation of existing Aβ fibrils by baicalein." Chinese Chemical Letters **23**(5): 595-598.

Soumyanath, A., Y. P. Zhong, E. Henson, T. Wadsworth, J. Bishop, B. G. Gold and J. F. Quinn (2012). "Centella asiatica Extract Improves Behavioral Deficits in a Mouse Model of Alzheimer's Disease: Investigation of a Possible Mechanism of Action." Int J Alzheimers Dis **2012**: 381974.

Srivareerat, M., T. T. Tran, S. Salim, A. M. Aleisa and K. A. Alkadhi (2011). "Chronic nicotine restores normal Aβ levels and prevents short-term memory and E-LTP impairment in Aβ rat model of Alzheimer's disease." Neurobiology of Aging **32**(5): 834-844.

Subramaniam, R., T. Koppal, M. Green, S. Yatin, B. Jordan, J. Drake and D. A. Butterfield (1998). "The free radical antioxidant vitamin E protects cortical synaptosomal membranes from amyloid beta-peptide(25-35) toxicity but not from hydroxynonenal toxicity: relevance to the free radical hypothesis of Alzheimer's disease." Neurochem Res **23**(11): 1403-1410.

Sugihara, N., T. Arakawa, M. Ohnishi and K. Furuno (1999). "Anti- and pro-oxidative effects of flavonoids on metal-induced lipid hydroperoxide-dependent lipid peroxidation in cultured hepatocytes loaded with α-linolenic acid." Free Radical Biology and Medicine **27**(11–12): 1313-1323.

Sung, S., Y. Yao, K. Uryu, H. Yang, V. M. Lee, J. Q. Trojanowski and D. Pratico (2004). "Early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease." FASEB J **18**(2): 323-325.

Szaniszlo, P., P. German, G. Hajas, D. N. Saenz, M. Kruzel and I. Boldogh (2009). "New insights into clinical trial for Colostrinin in Alzheimer's disease." J Nutr Health Aging **13**(3): 235-241.

Tabet, N., D. Mantle, Z. Walker and M. Orrell (2002). "Endogenous antioxidant activities in relation to concurrent vitamins A, C, and E intake in dementia." International Psychogeriatrics **14**(1): 7-15.

Takata, K., Y. Kitamura, M. Saeki, M. Terada, S. Kagitani, R. Kitamura, Y. Fujikawa, A. Maelicke, H. Tomimoto, T. Taniguchi and S. Shimohama (2010). "Galantamine-induced amyloid-β clearance mediated via stimulation of microglial nicotinic acetylcholine receptors." Journal of Biological Chemistry **285**(51): 40180-40191.

Tang, M. K. and J. T. Zhang (2001). "Salvianolic acid B inhibits fibril formation and neurotoxicity of amyloid beta-protein in vitro." Acta Pharmacol Sin **22**(4): 380-384.

Tang, Y., D. Huang, M. H. Zhang, W. S. Zhang, Y. X. Tang, Z. X. Shi, L. Deng, D. H. Zhou and X. Y. Lu (2016). "Salvianolic acid B inhibits Aβ generation by modulating BACE1 activity in SH-SY5Y-APPsw cells." Nutrients **8**(6).

Tanzi, R. E., R. D. Moir and S. L. Wagner (2004). "Clearance of Alzheimer's Abeta peptide: the many roads to perdition." Neuron **43**(5): 605-608.

Thapa, A., S. D. Jett and E. Y. Chi (2016). "Curcumin Attenuates Amyloid-β Aggregate Toxicity and Modulates Amyloid-β Aggregation Pathway." ACS Chemical Neuroscience **7**(1): 56-68.

Tippmann, F., J. Hundt, A. Schneider, K. Endres and F. Fahrenholz (2009). "Up-regulation of the α-secretase ADAM10 by retinoic acid receptors and acitretin." FASEB Journal **23**(6): 1643-1654.

Tsai, F. S., L. Y. Wu, S. E. Yang, H. Y. Cheng, C. C. Tsai, C. R. Wu and L. W. Lin (2015). "Ferulic acid reverses the cognitive dysfunction caused by amyloid β peptide 1-40 through anti-oxidant activity and cholinergic activation in rats." American Journal of Chinese Medicine **43**(2): 319-335.

Tsvetkova, D., D. Obreshkova, D. Zheleva-Dimitrova and L. Saso (2013). "Antioxidant activity of galantamine and some of its derivatives." Current Medicinal Chemistry **20**(36): 4595-4608.

Uğuz, A. C., A. Öz and M. Naziroğlu (2016). "Curcumin inhibits apoptosis by regulating intracellular calcium release, reactive oxygen species and mitochondrial depolarization levels in SH-SY5Y neuronal cells." Journal of Receptors and Signal Transduction **36**(4): 395-401.

Ullah, F., T. Ali, N. Ullah and M. O. Kim (2015). "Caffeine prevents d-galactose-induced cognitive deficits, oxidative stress, neuroinflammation and neurodegeneration in the adult rat brain." Neurochemistry International **90**: 114-124.

Utsuki, T., M. Shoaib, H. W. Holloway, D. K. Ingram, W. C. Wallace, V. Haroutunian, K. Sambamurti, D. K. Lahiri and N. H. Greig (2002). "Nicotine lowers the secretion of the Alzheimer's amyloid β-protein precursor that contains amyloid β-peptide in rat." Journal of Alzheimer's Disease **4**(5): 405-415.

Valizadeh, Z., A. Eidi, A. Sarkaki, Y. Farbood and P. Mortazavi (2012). "Dementia type of Alzheimer's disease due to beta-amyloid was improved by Gallic acid in rats." Healthmed **6**(11): 3648-3656.

Veerendra Kumar, M. H. and Y. K. Gupta (2003). "Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats." Clinical and Experimental Pharmacology and Physiology **30**(5-6): 336-342.

Verdile, G., S. Fuller, C. S. Atwood, S. M. Laws, S. E. Gandy and R. N. Martins (2004). "The role of beta amyloid in Alzheimer's disease: still a cause of everything or the only one who got caught?" Pharmacol Res **50**(4): 397-409.

Walsh, D. M. and D. J. Selkoe (2007). "A beta oligomers - a decade of discovery." J Neurochem **101**(5): 1172-1184.

Wang, C., L. Xu, F. Cheng, H. Wang and L. Jia (2015). "Curcumin induces structural change and reduces the growth of amyloid-β fibrils: A QCM-D study." RSC Advances **5**(38): 30197-30205.

Wang, J. B., Y. M. Wang and C. M. Zeng (2011). "Quercetin inhibits amyloid fibrillation of bovine insulin and destabilizes preformed fibrils." Biochem Biophys Res Commun **415**(4): 675-679.

Wang, P., C. Su, R. Li, H. Wang, Y. Ren, H. Sun, J. Yang, J. Sun, J. Shi, J. Tian and S. Jiang (2014). "Mechanisms and effects of curcumin on spatial learning and memory improvement in APPswe/PS1dE9 mice." Journal of Neuroscience Research **92**(2): 218-231.

Weggen, S., J. L. Eriksen, P. Das, S. A. Sagi, R. Wang, C. U. Pietrzik, K. A. Findlay, T. E. Smith, M. P. Murphy, T. Bulter, D. E. Kang, N. Marquez-Sterling, T. E. Golde and E. H. Koo (2001). "A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity." Nature **414**(6860): 212-216.

Wei, D., J. Tang, W. Bai, Y. Wang and Z. Zhang (2014). "Ameliorative effects of baicalein on an amyloid-β induced Alzheimer's disease rat model: A proteomics study." Current Alzheimer Research **11**(9): 869-881.

Wenk, G. L. (2003). "Neuropathologic changes in Alzheimer's disease." J Clin Psychiatry **64 Suppl 9**: 7-10.

Wilcock, G. K. and M. M. Esiri (1982). "Plaques, tangles and dementia. A quantitative study." J Neurol Sci **56**(2-3): 343-356.

Wobst, H. J., A. Sharma, M. I. Diamond, E. E. Wanker and J. Bieschke (2015). "The green tea polyphenol (-)-epigallocatechin gallate prevents the aggregation of tau protein into toxic oligomers at substoichiometric ratios." FEBS Letters **589**(1): 77-83.

Wu, Z., L. Zhao, X. Chen, X. Cheng and Y. Zhang (2015). "Galantamine attenuates amyloid-beta deposition and astrocyte activation in APP/PS1 transgenic mice." Exp Gerontol **72**: 244-250.

Wyss-Coray, T. (2006). "Inflammation in Alzheimer disease: driving force, bystander or beneficial response?" Nat Med **12**(9): 1005-1015.

Xiao, X. Q., R. Wang, Y. F. Han and X. C. Tang (2000). "Protective effects of huperzine A on beta-amyloid(25-35) induced oxidative injury in rat pheochromocytoma cells." Neurosci Lett **286**(3): 155-158.

Xiao, X. Q., H. Y. Zhang and X. C. Tang (2002). "Huperzine A attenuates amyloid beta-peptide fragment 25-35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation." J Neurosci Res **67**(1): 30-36.

Xiao, X. Q., H. Y. Zhang and X. C. Tang (2002). "Huperzine A attenuates amyloid β-peptide fragment 25-35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation." Journal of Neuroscience Research **67**(1): 30-36.

Xiong, Z., Z. Hongmei, S. Lu and L. Yu (2011). "Curcumin mediates presenilin-1 activity to reduce beta-amyloid production in a model of Alzheimer's Disease." Pharmacol Rep **63**(5): 1101-1108.

Xu, D. and C. Zhou (2010). "Antioxidative effects of berberine pre-treatment on hydrogen peroxide-induced PC12 cell toxicity." Neural Regeneration Research **5**(18): 1391-1395.

Xu, J., H. Zhang, F. Yang and J. X. Yu (2013). "Intervention effect of berberine on expressions of TNF-α and receptor type I in Aβ25-35-induced inflammatory reaction in SH-SY5Y cell lines." Zhongguo Zhongyao Zazhi **38**(9): 1327-1330.

Xu, X. H. (2003). "[Effects of puerarin on fatty superoxide in aged mice induced by D-galactose]." Zhongguo Zhong Yao Za Zhi **28**(1): 66-69.

Xu, Y., J. Shen, X. Luo, W. Zhu, K. Chen, J. Ma and H. Jiang (2005). "Conformational transition of amyloid beta-peptide." Proc Natl Acad Sci U S A **102**(15): 5403-5407.

Yan, J. J., J. S. Jung, T. K. Kim, M. A. Hasan, C. W. Hong, J. S. Nam and D. K. Song (2013). "Protective effects of ferulic acid in amyloid precursor protein plus presenilin-1 transgenic mouse model of Alzheimer disease." Biological and Pharmaceutical Bulletin **36**(1): 140-143.

Yang, F., G. P. Lim, A. N. Begum, O. J. Ubeda, M. R. Simmons, S. S. Ambegaokar, P. P. Chen, R. Kayed, C. G. Glabe, S. A. Frautschy and G. M. Cole (2005). "Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo." J Biol Chem **280**(7): 5892-5901.

Yang, Y., M. Liang, Z. Jia, B. Lu and D. Feng (2015). "Investigation of anti-neuroinflammation and protection mechanism of curcumin in alzheimer's disease." Medical Journal of Wuhan University **36**(3): 332-336.

Yatin, S. M., M. Yatin, T. Aulick, K. B. Ain and D. A. Butterfield (1999). "Alzheimer's amyloid β-peptide associated free radicals increase rat embryonic neuronal polyamine uptake and ornithine decarboxylase activity: Protective effect of vitamin E." Neuroscience Letters **263**(1): 17-20.

Yokozawa, T., A. Ishida, Y. Kashiwada, E. J. Cho, H. Y. Kim and Y. Ikeshiro (2004). "Coptidis Rhizoma: protective effects against peroxynitrite-induced oxidative damage and elucidation of its active components." J Pharm Pharmacol **56**(4): 547-556.

Yu, G., Q. Tian, R. Liu, Q. Wang, J. Z. Wang and X. Wang (2011). "Berberine attenuates calyculin A-induced cytotoxicity and tau hyperphosphorylation in HEK293 cells." Journal of Alzheimer's Disease **24**(3): 525-535.

Zhang, C., A. Browne, D. Child and R. E. Tanzi (2010). "Curcumin decreases amyloid-beta peptide levels by attenuating the maturation of amyloid-beta precursor protein." J Biol Chem **285**(37): 28472-28480.

Zhang, C., A. Browne, D. Child and R. E. Tanzi (2010). "Curcumin decreases amyloid-β peptide levels by attenuating the maturation of amyloid-β precursor protein." Journal of Biological Chemistry **285**(37): 28472-28480.

Zhang, J. X., J. G. Xing, L. L. Wang, H. L. Jiang, S. L. Guo and R. Liu (2017). "Luteolin inhibits fibrillary β-amyloid1-40 -induced inflammation in a human blood-brain barrier mode by suppressing the p38 MAPK-mediated NF-єκB signaling pathways." Molecules **22**(3).

Zhang, S. Q., D. Obregon, J. Ehrhart, J. Deng, J. Tian, H. Hou, B. Giunta, D. Sawmiller and J. Tan (2013). "Baicalein reduces beta-amyloid and promotes nonamyloidogenic amyloid precursor protein processing in an Alzheimer's disease transgenic mouse model." J Neurosci Res **91**(9): 1239-1246.

Zhang, X., J. Hu, L. Zhong, N. Wang, L. Yang, C. C. Liu, H. Li, X. Wang, Y. Zhou, Y. Zhang, H. Xu, G. Bu and J. Zhuang (2016). "Quercetin stabilizes apolipoprotein e and reduces brain Aβ levels in amyloid model mice." Neuropharmacology **108**: 179-192.

Zhang, X., L. Si, X. Shi, W. Yin and Y. Li (2010). "Curcumin inhibits beta-amyloid protein 40/42 expression in the brain in a concentration- and time-dependent manner." Neural Regeneration Research **5**(16): 1205-1210.

Zhang, X., J. Y. Sun, H. M. Zhang, L. Si and Y. Li (2013). The regulation of natural food dyes curcumin on the amyloidogenic pathway of APP. Advanced Materials Research. **781-784:** 1160-1163.

Zhang, X., H. Zhang, L. Si and Y. Li (2011). "Curcumin mediates presenilin-1 activity to reduce β-amyloid production in a model of Alzheimer's disease." Pharmacological Reports **63**(5): 1101-1108.

Zhang, Y., L. Cui, Y. Zhang, H. Cao, Y. Wang, T. Teng, G. Ma, Y. Li and K. Li (2013). "Ferulic acid inhibits the transition of amyloid-β42 monomers to oligomers but accelerates the transition from oligomers to fibrils." Journal of Alzheimer's Disease **37**(1): 19-28.

Zhang, Z. X., Y. B. Li and R. P. Zhao (2017). "Epigallocatechin Gallate Attenuates β-Amyloid Generation and Oxidative Stress Involvement of PPARγ in N2a/APP695 Cells." Neurochemical Research **42**(2): 468-480.

Zhao, G., C. Yao-Yue, G. W. Qin and L. H. Guo (2012). "Luteolin from Purple Perilla mitigates ROS insult particularly in primary neurons." Neurobiology of Aging **33**(1): 176-186.

Zhao, H. F., N. Li, Q. Wang, X. J. Cheng, X. M. Li and T. T. Liu (2015). "Resveratrol decreases the insoluble Aβ1-42 level in hippocampus and protects the integrity of the blood-brain barrier in AD rats." Neuroscience **310**: 641-649.

Zhao, L., J.-L. Wang, R. Liu, X.-X. Li, J.-F. Li and L. Zhang (2013). "Neuroprotective, Anti-Amyloidogenic and Neurotrophic Effects of Apigenin in an Alzheimer's Disease Mouse Model." Molecules **18**(8): 9949.

Zhao, S. S., W. N. Yang, H. Jin, K. G. Ma and G. F. Feng (2015). "Puerarin attenuates learning and memory impairments and inhibits oxidative stress in STZ-induced SAD mice." NeuroToxicology **51**: 166-171.

Zheng, K., X. Dai, N. Xiao, X. Wu, Z. Wei, W. Fang, Y. Zhu, J. Zhang and X. Chen (2017). "Curcumin Ameliorates Memory Decline via Inhibiting BACE1 Expression and β-Amyloid Pathology in 5×FAD Transgenic Mice." Molecular Neurobiology **54**(3): 1967-1977.

Zheng, L. T., J. Ock, B. M. Kwon and K. Suk (2008). "Suppressive effects of flavonoid fisetin on lipopolysaccharide-induced microglial activation and neurotoxicity." International Immunopharmacology **8**(3): 484-494.

Zheng, N., P. Yuan, C. Li, J. Wu and J. Huang (2015). "Luteolin Reduces BACE1 Expression through NF-κB and Estrogen Receptor Mediated Pathways in HEK293 and SH-SY5Y Cells." Journal of Alzheimer's Disease **45**(2): 659-671.

Zhou, F., S. Chen, J. Xiong, Y. Li and L. Qu (2012). "Luteolin reduces zinc-induced tau phosphorylation at Ser262/356 in an ROS-dependent manner in SH-SY5Y cells." Biol Trace Elem Res **149**(2): 273-279.

Zhou, Y., N. Xie, L. Li, Y. Zou, X. Zhang and M. Dong (2014). "Puerarin alleviates cognitive impairment and oxidative stress in APP/PS1 transgenic mice." International Journal of Neuropsychopharmacology **17**(4): 635-644.

Zhu, F., F. Wu, Y. Ma, G. Liu, Z. Li, Y. Sun and Z. Pei (2011). "Decrease in the production of beta-amyloid by berberine inhibition of the expression of beta-secretase in HEK293 cells." BMC Neuroscience **12**.

Zhu, F., F. Wu, Y. Ma, G. Liu, Z. Li, Y. Sun and Z. Pei (2011). "Decrease in the production of beta-amyloid by berberine inhibition of the expression of beta-secretase in HEK293 cells." BMC Neurosci **12**: 125.

Zhu, L. H., W. Bi, R. B. Qi, H. D. Wang and D. X. Lu (2011). "Luteolin inhibits microglial inflammation and improves neuron survival against inflammation." Int J Neurosci **121**(6): 329-336.