Cinnamon, a promising prospect towards Alzheimer's disease

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Abstract

In the last decades, an exponential increase of efforts concerning the treatment of Alzheimer's disease (AD) has been practiced. Phytochemicals preparations have a millenary background to combat various pathological conditions. Various cinnamon species and their biologically active ingredients have renewed the interest towards the treatment of patients with mild-to-moderate AD through the inhibition of tau protein aggregation and prevention of the formation and accumulation of amyloid-β peptides into the neurotoxic oligomeric inclusions, both of which are considered to be the AD trademarks. In this review, we presented comprehensive data on the interactions of a number of cinnamon polyphenols (PPs) with oxidative stress and pro-inflammatory signaling pathways in the brain. In addition, we discussed the potential association between AD and diabetes, vis-à-vis the effluence of cinnamon PPs. Further, an upcoming prospect of AD epigenetic pathophysiological conditions and cinnamon has been sighted. Data was retrieved from the scientific databases such as PubMed database of the National Library of Medicine, Scopus and Google Scholar without any time limitation. The extract of cinnamon efficiently inhibits tau accumulations and Aβ aggregation and toxicity *in vivo* and *in vitro* models. Indeed, cinnamon possesses neuroprotective effects interfering multiple oxidative stress and pro-inflammatory pathways. Besides, cinnamon modulates endothelial functions and attenuates the vascular cell adhesion molecules. Cinnamon PPs may induce AD epigenetic modifications. Cinnamon and in particular, cinnamaldehyde seem to be effective and safe approaches for treating and prevention of AD onset and/ or progression. However, further molecular and translational research studies as well as prolonged clinical trials are required to establish the therapeutic safety and efficacy in different cinnamon *spp.*

Keywords: cinnamon, Alzheimers disease, neurocognitive performance, cellular pathway

Abbreviations

AD, Alzheimer's disease; PPs, polyphenols; EGCG, epigalocatechingallate; NFTs, neurofibrillary tangles; ACh, acetylcholine; Aβ, amyloid-beta; APP, amyloid precursor protein; PS-1, presenilin-1; PS-2, presenilin-2; AChE, acetylcholine esterase; NaB, sodium benzoate; BBB, blood brain barrier; LPS, Lipopolysaccharide; PNC, (2R, 3S)-pinobanksin-3-cinnamate; MDA, malondealdehyde; SOD, superoxide dismutase; PD, Parkinson disease; NFs, neurotrophic factors; GABRA5, Gamma-Aminobutyric Acid Type A Receptor Alpha5 Subunit; CREB, cAMP response element binding protein; FRAP, ferric reducing antioxidant power; SH, plasma thiol; CAT, catalase; LPO, lipid peroxidation, MAPK, mitogen-activated protein kinase; ARE; antioxidant responsive element, NF-κB, nuclear factor-kappaB; ERK, extracellular signal-regulated kinase; MEK, feedback-regulate cellular; NIK, NF-κB inducing kinase; JNK, c-Jun N-terminal kinase; SIRT, sirtuin; IFN, interferons; IL, interleukins; COX, cyclooxygenase; iNOS, Inducible nitric oxide synthase; NO, nitric oxide; LPS, lipopolysaccharide; TLR4, ligand-induced toll-like receptor 4; TDI, tolerable daily intake; LD_{50}, 50% lethal dose; PKA, protein kinase A; PHFs, paired helical filaments; cAMP, cyclic AMP; BDNF, brain derived neurotrophic factor; RAGE, receptors for advanced glycation end-products; LRP-1, lipoprotein receptor-related protein 1; P-gp, P-glycoprotein; VCAM-1, vascular cell adhesion molecule-1; VEGFR, vascular endothelial growth factor receptor; sICAM-1, soluble intercellular adhesion molecule-1; Nrf2; nuclear factor (Erythroid-Derived 2)-Like 2; HDAC, histone methyltransferases; USFDA, United States Food and Drug Administration; GRAS, generally recognized as safe; DPPH, 2,2-diphenyl-1-picrylhydrazyl

1. Introduction

According to the World Alzheimer Report 2016, there were 46.8 million people worldwide encountering dementia in 2015 and this number will ascend to 131.5 million in 2050 (Dementia statistics, 2016). Observational data strongly support the association between genetic and human lifestyle to develop such conditions. Many clinical trials have shown that early intervention and treatment are the only way to slow or maybe reverse the progression of the disease, since the current therapies mostly possess symptomatic properties with surplus side effects and insufficient effectiveness. Concurrently, dietary components were found to impress the incidence, severity and management of many health issues such as; chronic diseases, diabetes and cognitive impairments (Ibrahim et al., 2017). Alzheimer's disease (AD) is characterized as a subgroup of a progressive age-related neurodegenerative disorders and as the most prevalent type of dementia. In a simple definition, AD is triggered by the distinct protein inclusions that presumably can confer synaptic/neuronal dysfunctions (Haass and Selkoe, 2007). In the brain of patients with AD, in addition to atrophy, nerve and synapse loss, deposition of the extracellular amyloid/senile plaques and formation of an excessive level of hyperphosphorylated intracellular neurofibrillary tangles (NFTs) containing microtubule-associated tau protein, are perceived. Rather than amyloid plaques, NFTs and by some classification hippocampal acetylcholine (ACh) decline, several other structural and functional modifications such as inflammatory responses and oxidative stresses seize critical impressions on pathological alterations in the AD (Fernández-Bachiller et al., 2009; Wyss-Coray, 2006).

Basically, amyloid plaques have been structured of amyloid-beta (Aβ) containing 39 to 42 amino-acid peptides that results from the sequential cleavage of the β-amyloid precursor protein (APP) by three proteases including α-, β- and γ-secretase. Aβ is capable of self-aggregation, and at high concentration forms very toxic monomeric and oligomeric structures. The Aβ42/Aβ40 ratio manipulates the formation of amyloid plaques, particularly by increasing the production of the toxic plaque-promoting Aβ42 peptide and this ratio can be amplified by mutations/changes in three different genes such as APP on chromosome 21, presenilin-1 (PS1) on chromosome 14 and PS2 on chromosome 1, which are mainly involved in AD (Haass and Selkoe, 2007). To defeat AD, up to date, Aβ inhibitors are either targeting Aβ generation or oligomerization and are supposed as the focal potential treatments. Therefore, therapeutic strategies should mainly focus to restrain either β- or γ-secretase that lessen Aβ production or aggregation, or by factors that increase its removal as by some means. AD was described as a result of an imbalance between Aβ production and Aβ clearance (LaFerla et al., 2007; Robert, 2004). In between, the enzyme acetylcholine esterase (AChE) plays a key role and facilitates the synthesis, deposition and aggregation of toxic Aβ. Accordingly, AChE interacts with Aβ and interrupts cholinergic transmission at the cholinergic synapses by rapid hydrolysis of ACh, leading to the cognitive impairment in AD. Thus, inhibition of AChE presumes as a strategy for AD management, because of an enhancement in cholinergic function in the brain regions and a decrease in the deposition of Aβ (Hasani-Ranjbar et al., 2010; Mukherjee et al., 2007).

Besides Aβ and AChE, tau or axonal protein (also found in somatodendritic compartments and oligodendrocytes) plays crucial in AD development. Under normal conditions, the stabilization, regulation, function and assembly of microtubules in neural cells (central and peripheral nervous system) is correlated with tau. Broadly, these microtubules facilitate the transportation of the proteins and neurotransmitters that have been synthesized within the

cell towards the synapses; those are mainly correlated with cognitive functions. The balance between assembly and disassembly of these microtubules is synchronized by tau, in this way the stability and the integrity of neurons is regularly maintained. Thus, the abnormal activity of tau is linked with AD progression and also to the activity of enzymes such as Cdk5 and GSK3. Both Aβ and tau induce toxicity in AD via the procedures that are fully regulated by different kinases and phosphatases (Chauhan, 2006).

Once tau is hyperphosphorylated, detaches from microtubules, accumulates in the somatodendritic compartment of neurons, in which modifies normal neuronal functions, morphology and viability. Subsequently, tau proteins are aggregated and eventually form NFTs and neuropil threads (Ittner and Götz, 2011). Regularly, these tangles are formed in the late stages of AD in association with amyloid formation (Peterson et al., 2009). The amount of NFTs has also been linked to the severity of dementia in AD (Arriagada et al., 1992). It has been proposed that hyperphosphorylated tau may contribute in neuronal dysfunction even before its deposition (Shankar et al., 2008). Another way, tau is known to regulate neuronal excitability and hyperphosphorylated tau suppresses pre-synaptic protein expression and cause the dysfunctional regulation of neuronal signaling and synaptic function that contribute AD (Morris et al., 2011; Cárdenas et al., 2012). Plethora studies pointed out that phosphorylated tau is essential for Aβ-induced neurotoxicity and cognitive decline (Amadoro et al., 2011; Roberson et al., 2007). In 2011, Ittner and Götz proposed the augmentation in the concentration of tau within the dendrites, increased the chance of neurons to be more susceptible to the damages caused by Aβ in the postsynaptic dendrites. Therefore, combinatorial approaches, which target both tau and Aβ proteins, emerge prudent.

As yet, plant-derived bioactive phytochemicals have been speculated to perform various neuroprotective and neuroregenerative actions. Table 1 indicates a comprehensive list of

the plant species capable to ameliorate AD and brain conditions, those trap tau or Aβ proteins from aggregation and also AChE inhibitors. More to the point, the evidence supports the nutritional interventions for AD. To explain, the level of oxidative stress is implicated to the diet regimen, and also oxidative stress is known as a potential cause of AD. Further, dietary restriction may extend the resistance of neuronal dysfunction (Mattson, 2000). With respect to AD, in this review we have intended to highlight the neuroprotectivity posture of cinnamon and its bioactive derivatives to modulate the upstream contributing mediators of AD. Also, the bioavailability and clinical application of cinnamon and its ingredients along with the promising prospect of the possible interactions between cinnamon, AD and related epigenetic mechanisms, is discussed.

2. Cinnamon

The genus *Cinnamomum* belongs to the Lauraceae family with nearly 250 species several are known as spices. Cinnamon is a well plant worldwide and applies as a generic term that mainly covers 2 plant species; (*Cinnamomum verum* J.S. Presl/ *C. zeylanicum* Nees/ Ceylon cinnamon/ true cinnamon/ Mexican cinnamon) and (*C. cassium* Blume/ *C. aromaticum* Nees/ Chinese cinnamon/ cassia) (Chen *et al.*, 2014b). Similarly, some other species appealed commercial interests, for example; *C. burmannii* (Indonesian cassia), *C. tamala* (Indian cassia), *C. bejolghota, C. osmophloeum* and *C. loureiroi* Ness (Vietnamese cinnamon). Common cinnamon is a spice (in form of sticks or powder) obtained from the brown inner bark of a number of evergreen trees and shrubs from this genus. Cinnamon is widely distributed in Sri Lanka, and currently, the coastal region of this country, approximately affords most of the cinnamon used around the world. Cinnamon bioactive compounds possess potent therapeutic efficiency in diabetes (Blevins et al., 2007; Cao et al., 2007; Lee et al., 2013), cancer (Koppikar et al., 2010; Unlu et al., 2010), oxidative

stress (Rao and Gan, 2014), cardiovascular disease (Hwa et al., 2012), wound healing (Kamath et al., 2003), inflammatory syndromes, cholesterol levels and immunomodulatory diseases (Jayaprakasha and Rao, 2011; Qadir et al., 2017). Additionally, cinnammon preparations were being used traditionally for centuries because of their neurostimulant, carminative, antibacterial and antifungal properties (Chanotiya and Yadav, 2010; Gende et al., 2008; Rao and Gan, 2014) (Fig. 1). Only during the past decade, scientists devoted to explore the neuroprotective/ neurodegenerative aspects of cinnamon, notwithstanding it was shown that multidisciplinary mechanisms are involved in this regard (Anderson et al., 2013; Frydman-Marom et al., 2011; Peterson et al., 2009).

Cinnamon is reputed from both nutritional and pharmacological points of the view. The beneficial health promoting properties of cinnamon is mainly attributed to its polyphenolic composition and the volatile essential oils coming from the different parts of the plant (bark, leaves, flowers, or buds). The cinnamon bark essential oils such as cinnamate, cinnamic acid, cinnamic aldehyde and cinnamylaldehyde and eugenol are the major components of the leaves, camphor is the main compound in roots. Coumarins, phenolic acids, terpenes, tannins, mucus and carbohydrates were identified to be biologically active (Ooi et al., 2006; Singletary, 2008). Catechin and epigallocatechingallate (EGCG) were found to be the major phenolic compounds in cinnamon (mostly responsible for its antioxidant potential), whereas cinnamylaldehyde is the main compound of volatile oils (Table 2). In order to the nutritional values, ground cinnamon approximately encompasses 11% water, 81% carbohydrates (including 53% dietary fiber), 4% protein and 1% saturated fatty acids. In addition, cinnamon contains valuable amounts of protein, fibre, vitamins and minerals (Ca, P, Na, K and Fe) (US National Nutrient Database., 2016).

There is no major concern about the safety and toxicity of cinnamon *spp*. According to United State Food and Drug Administration (USFDA), cinnamon has GRAS (generally

recognized as safe) status as a food additive (Barceloux, 2008). Medicinal amounts of cinnamon were reported safe, but it may become questionable when is used in excessive doses or over a long term (Dugoua et al., 2007). No adverse reports have been cited in all the human studies involving cinnamon or the aqueous extracts of cinnamon (Anderson, 2008). Acute oral toxicity assay showed Ceylon cinnamon extract was safe at doses below 0.5 g/kg/bw, once was fed to Wistar rats (Ahmad et al., 2015). Administration of C. zeylanicum (100, 200 and 400 mg/kg/bw; comparable to a human adult dose of 600-2400 mg/kg/bw) did not induce significant behavioral changes in terms of excitement, nervousness, dullness, alertness, ataxia or death in rats (Anand et al., 2010). Cinnamon bark oil may cause skin sensitization, which limits its utilization in cosmetic and topical products (Hartmann and Hunzelmann, 2004). While cinnamon bark is famed more in causing drug interactions with hypoglycemic medicines, potential interactions with blood thinners such as warfarin and aspirin is labeled as significant and may raise bleeding and bruising in patients taking warfarin and cinnamon bark, thus it should be monitored closely (RxList, 2017a,b).

Mass spectrometric analysis has indicated that *C. verum* is much more pure than *C. cassia*, thus the daily consumption of *C. cassia* high quantities might be risky. *C. verum* contains coumarins only as trace elements. Although, cinnamaldehyde is the major component of both species, *C. cassia* contains some hepatotoxic 1-benzopyran-2-one or coumarin (Jana et al., 2013; Ooi et al., 2006). Today, coumarin is considered as a non-genotoxic compound with carcinogenic effect, as it might show hepatotoxic effect in sensitive groups (Abraham et al., 2010) High coumarin content of *C. cassia* may raise some safety concerns over prolonged consumption, but short-term trials have not reported any undesired effects (Wang et al., 2013). In 2008, the European Regulation (EC) No 1334/2008 lined maximum limits for coumarin should not exceed; 50 mg/kg/bw in bakery, 20 mg/kg/bw in breakfast

cereals and 5 mg/kg/bw in desserts, with a reference to cinnamon in the labeling (Regulation, 2008). The Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food (AFC) concluded that exposure to coumarin at doses 3 times higher than the Tolerable Daily Intake (TDI) for one to two weeks is not of safety concern (EFSA, 2008). In a clinical study (24 human individuals), it was surveyed that upon cinnamon intake (coumarin dose of 12 mg), coumarin was detected in plasma and urine, but did not reach the TDI of 0.1 mg/kg/bw daily for risk assessment of coumarin exposure from cinnamon-containing sources (Abraham et al., 2011)

In the body, cinnamaldehyde is converted into cinnamic acid by oxidation, as in the liver, this compound is β-oxidized to benzoate in the form of sodium salt or benzoyl-CoA (Khasnavis and Pahan, 2012). USFDA and the council of Europe have approved cinnamaldehyde is a safe natural ingredient (daily intake of 1.25 mg/kg/bw), but its high and non-nutritional consumption may cause genotoxicity and hepatotoxicity as proven by *in vivo* and *in vitro* assays (Zhu et al., 2017). It was demonstrated that the 50% median lethal dose (LD_{50}) of cinnamaldehyde (from *C. zeylanicum*) was 1850±37 mg/kg/bw in Wistar rats (Babu et al., 2007). This would be comparable with 11.4±0.2 g/kg/bw in adult human (Ranasinghe et al., 2012). Cinnamaldehyde has been characterized as a strong dermal sensitizer and a mucous membrane irritant (Barceloux, 2008). Yet, there is no established dosage to indicate how much cinnamon might be toxic to human, however high concentration could be toxic.

3. Cinnamon and neurocognitive function

There are certain compounds that have been reported in many studies those have the potential to inhibit the formation of Aβ plaques. It has been stated that cinnamon extract can interact with Aβ peptide at the initial stage of self-aggregation via polyphenol entity in

order to inhibit its aggregation, and hence inhibit the Aβ toxicity (Frydman-Marom et al., 2011). Cinnamon inhibited the formation, accumulation and toxic effects of Aβ plaques in PC12 neuronal cells. PC12 cell viability was reported about 100% along with a dose dependent inhibition of the cytotoxic effect of $A\beta_{42}$ fibrils, once the ratio of cinnamon extract and $A\beta_{40}$ concentration was 2: 1 (40: 20 µg/ml) (Frydman-Marom et al., 2011). Similar results were achieved whilst aqueous cinnamon extract (0.75 mg/ml) potentially inhibited the oligomer and amyloid fibril formation in AD fly models. In a same study, cinnamon extract reduced the plaque formation after oral administration (100 µg/ml for 120 days) in AD transgenic mouse models, hence significant improvement in animal's cognitive behavior was observed. It was postulated that cinnamon compounds may either cross the blood brain barrier (BBB) or probably pass through other peripheral routes (Frydman-Marom et al., 2011). Both extracellular plaques and intracellular NFTs accelerate AD. Moreover, cinnamon has shown to improve those factors which are associated with AD and memory loss through blocking tau formation and ultimately inhibited the effects shown by the accumulation of amyloid precursor protein (Frydman-Marom et al., 2011).

An aqueous extract of *C. zeylanicum* (0.11 mg/ml) efficiently inhibited human tau accumulation, induced dissociation of tau tangles (*C. zeylanicum* concentration was 0.22 mg/ml) and unraveling of paired helical filaments (PHFs) by prevention of the assembly of free tubulin into microtubules or filament formation in AD brain. Indeed, the normal function of tau and the accumulation of free tubulin microtubules were not disrupted by the extract. A-type doubly linked procyanidin oligomers and cinnamaldehyde were considerably responsible for such inhibitory activity (Peterson et al., 2009).

George and teammates proposed that some small molecules are able to form a reversible interaction with the cysteinyl residues of tau, accordingly may prevent tau tangles from

aberrant alterations. In addition, they found that the oxidized form of epicatechin and cinnamaldehyde (each of 110 µM) isolated from cinnamon extract, could inhibit tau aggregation through the same mechanism. Further, these compounds inhibited tau oxidation and subsequent formation of high molecular weight species that are believed to trigger tangle formation, thus prevented neuronal loss due to the oxidative stress. Into the bargain, pre-incubation of the tau 187 with cinnamaldehyde prior to initiation of aggregation was led to a greater retardation comparing to the time that cinnamaldehyde was introduced to the tau at the time of aggregation (George et al., 2013).

In vitro condition, HEK293 cells transfected with glycogen synthase kinase 3 (an enzyme responsible for phosphorylation of the tau protein) and tau protein were co-administrated with cinnamon extract for 48 h. The obtained results indicated cinnamon abrogated tau phosphorylation by attenuating the enzyme activity, perhaps via protein kinase A dependent phosphorylation (Donley et al., 2016).

An extract of *C. zeylanicum* (50 mg/kg/bw) was found more applicable for prevention therapy, since improved cognitive symptoms when was administrated at early stages of life in 2 months old non-transgenic rat model of AD. Cinnamon increased phosphorylated glycogen synthase kinase-3β (critical for choline metabolism), inhibited AChE activity and increased neuron number in hippocampus area of these animals (Madhavadas and Subramanian, 2016). The AChE inhibitory activity of the methanol extract of *C. tamala* and its leaf oil was explored, among this, cinnamon oil showed the higher AChE inhibition (IC_{50}: 45.88±1.94 µg/ml) than the *C. tamala* crude extract (IC_{50}: 77.78±0.03 µg/ml) (Dalai et al., 2014). Besides, coumarins were also found to possess AChE inhibitory properties (Anand et al., 2012).

PPs such as EGCG (frequently presented in cinnamon) and curcumin are also able to arrest amyloid fibrils and have the neuroprotective potential in curing AD and other

neurodegenerative disorders like Parkinson disease (PD) (Lesné et al., 2006; Shoval et al., 2008; Khan et al., 2016; Panickar et al., 2009). Cinnamyl alcohol (100 mg/ml) has also been reported to show inhibitory effects against AChE activity (Park, 2014). Furthermore, Cinnamaldehyde prevented inflammation and suppressed the formation of NFs, thus enhanced cinnamaldehyde levels might manipulate the cognitive function in the scopolamine-induced amnesia in mouse models (Park et al., 2016). Trans-cinnamaldehyde has been investigated in animal models of ischemia induced brain injury, and it has been verified that this compound has a neuroprotective effect in the Lipopolysaccharide (LPS)-induced inflammation of BV-2 microglials. The cell viability was found to be 100%, where the concentration of compound was 12.5, 25 and 50 µM. Trans-cinnamaldehyde considerably reduced the infarction area (10–30 mg/kg/bw) and also decreases the level of iNOS protein expression in rat injured brain tissues (Chen et al., 2016).

In a similar study, the neuroprotective effects of (2R, 3S)-pinobanksin-3-cinnamate (PNC), in the rat model with occlusion damaged bilateral common carotid artery were investigated. They found that administration of PNC (5 and 10 mg/kg/bw) for a period of five weeks considerably enhanced the cognitive behavior of the rats suffering from dementia. Furthermore, they also proposed that PNC can lower the malondialdehyde (MDA) levels, improves the superoxide dismutase (SOD) activity and also lowers the release of cytochrome c. It has been concluded that PNC exhibited its neuroprotective activity via neutralizing the oxidative stress as a flavonoid and hence it can be used to treat the vascular dementia (Liu et al., 2015).

The protective actions of flavonoids enriched foods such as green tea, blueberry and cocoa are due to their interaction with several molecular and cellular targets. For example, flavonoids interact with cellular targets at the receptor level and this interaction leads to an enhancement in expression of proteins involved in neuroprotection. Moreover, the action

of these flavonoids on the vascular system may cause an improvement in the cognitive performance via increasing blood flow to the brain region and initiate neurogenesis in the brain hippocampus and hence it would slow down the progression of AD (Williams and Spencer, 2012). PNC probably alleviates the mitochondrial redox balance via scavenging reactive oxygen species (ROS) either directly or by lowering the ROS formation through shielding the electron transport chain (Lin et al., 2003). Proanthocyanidins are the recent subject of research (Wang et al., 2013) and are efficient scavengers of reactive oxygen species, therefore might be favorable for treatment of AD (Peng et al., 2008).

Cinnamic acid (45 and 90 mg/kg/bw for 21 days) was shown to improve depression, neuroinflammation and brain injury in rats (Yao et al., 2015). Considering a wide range of distribution in natural reserves, significant intake of dietary food products, as well as high and effective absorption rate from the intestine and the brain cells, cinnamic acid invokes as a promising candidate for treatment of neurological disorders (Zamora-Ros et al., 2016).

In a new approach, phenylpropanoid compounds (medioresinol and cryptamygin A (4 µg/ml of each)) isolated from cinnamon bark showed anti-amyloidogenic effects and targeted β-secretase and sAPPβ (the proteolytic fragment of APP catalyzed by β-secretase) and reduced Aβ40 production by inhibition of β-secretase in Chinese hamster ovarian (CHO) cells. These cells stably express amyloid precursor proteins (Kang et al., 2016). In sum, cinnamon *spp.* and its biologically active compounds target every 3 AD hallmarks; inhibition of AChE activity, abeta formation/ aggregation and tau phosphorylation.

4. Brain localization of cinnamon

When cinnamon are ingested to the body, it undergoes extensive metabolism both in the small and large intestine and in the liver as well, which results in the production of various derivatives, and these metabolites are different from those of parent compounds which can

be found in foods (Manach et al., 2005, Williamson and Manach, 2005). The ability of cinnamon to affect the nervous system will mostly depends on their metabolites ability to cross the BBB through the process of diffusion across the membrane and eventually enter the brain (Schaffer and Halliwell, 2012). It has been recommended that the capacity of cinnamon flavonoids and its metabolites to enter the brain upon crossing the BBB mostly depends on the extent of their lipophilicity (Lin et al., 2007). For example, those flavonoids which are less polar, such as methylated derivatives can enter the brain with much high concentration than those metabolites that are more polar such as glucuronides. But despite this fact, there are certain animal studies which show the entry of glucuronides entry into the brain through BBB (El Mohsen et al., 2002; Youdim et al., 2004).

It was stated that people with poor learning ability have a low level of GABRA5 and a high level of CREB, two important proteins located in the hippocampus region of the brain regarding learning and memory function. In order to explore cinnamon's effect on these proteins, the researchers arranged learning test in mice with diminished learning capacity. Following a month of cinnamon administration on a daily basis, they found a significant progression in their learning ability twice faster than before co-treatment with cinnamon (Modi et al., 2016). Similarly, it has been confirmed that cinnamon has the potential to stop the development of PD in a mouse model, which was associated to its metabolite NaB. NaB protects the neurons, normalizes the brain cells and hence enhances the communication power inside the brain (Rao and Gan, 2014). The application of cinnamon in such condition could stop the progression of neurodegenerative disorders in a safe manner and also it would be a significant improvement in curing such disorders (Modi et al., 2016).

There are other types of flavonoids which are functionally related to cinnamon such as epicatechin and catechin, and their glucuronidated metabolites that have been identified in

the brain after acute and chronic administration along with grape seed poly phenolic extracts (El Mohsen et al., 2002). In a study, it has been confirmed that only those polyphenols which are monomeric in fraction derived from grape like those of catechin and epicatechin can be only accumulated in the brain approximately up to 400 nM as compared to the other oligomeric fraction of the extract (Wang et al., 2012). They also demonstrated that a diet regimen enriched by proanthocyanidin, catechin and epicatechin in monomeric, oligomeric and polymeric forms could promote learning and memory in AD, but only the monomeric metabolites can selectively reach and accumulate in the brain in AD mouse model (Wang et al., 2012). It is important to know that metabolites belonging to various types of flavonoids accumulate in the brain by crossing the BBB and hence play their vital role in memory formation and learning skills, while these functions of the brain are adversely affected by ageing and degenerative diseases such as Alzheimer (Fazlullah Khan and Bishayee, 2016).

5. Cinnamon and cellular pathways in AD

5.1. Cinnamon and oxidative impairments

Cinnamon PPs exhibit neuroprotective effects in AD models through various intracellular mechanisms. The free radical theory of aging along with the fact that aging is the prime stressor of AD merits the implication of oxidative stress in the clinical progression of AD (Behl, 1997; Saeidnia and Abdollahi, 2013). In AD, oxidative impairments usually originate from mitochondrial dysfunction (formation of ROS and oxidative stress), from Aβ42 toxicity (production of ROS in the presence of metal ions; Fe^{2+} and Cu^{2+}) and from glial recruitment and activation (production of pro-inflammatory cytokines and excessive levels of superoxide and nitric oxide), thereby inspires calcium overload, excitotoxicity

and eventually leads to the apoptosis in neurons (Emerit et al., 2004). There are various studies that prove Aβ can generate oxidative stress and spreads its toxicity via redox activity, ionic homeostasis and hyperphosphorylation of tau (Ittner and Jurgen, 2011). In other hand, oxidative stress may raise the production of amyloid-β oligomers by activating an enzyme that limits Aβ production, so facilitates amyloid plaque formation (Devi et al., 2012). It was supposed that both oxidative stress and soluble Aβ oligomers induce pathways and kinases that are involved in tau phosphorylation like extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (JNK) (Moriss et al., 2011). Remarkably, PPs can counter Aβ aggregation and mediate cell signaling associated with Aβ-induced cellular responses by offsetting oxidative stress through their antioxidant abilities.

Cinnamon crude extract or its polyphenolic derivatives illustrated significant free radical scavenging activities via the alteration of oxidative stress enzymes or through the oxidative pathways to maintain redox homeostasis. Cinnamon increases ferric reducing antioxidant power (FRAP) and plasma thiol (SH), lowers MDA levels, and elevates antioxidant enzyme activities of SOD and catalase (CAT) (Moselhy and Ali, 2009; Roussel et al., 2009). In clinical studies, it was found that the consumption of cinnamon for a long period of time could significantly improve the blood markers of oxidative stress, for example total antioxidant capacity of serum is elevated, while the transaminase and lipid peroxidation (LPO) are reduced (Fani et al., 2008; Ranjbar et al., 2007; Rashidi et al., 2014). Recently, the levels of neurotoxicity, LPO and the catalytic activity of SOD and CAT were evaluated in fly (*Drosophila* melanogaster) model of neurodegeneration. The levels of lipid hydroperoxides were reduced in cinnamyl acetate and cinnamic acid treated groups, while higher levels were observed in cinnamaldehyde and ethyl cinnamate groups. They found out that cinnamon bioactive compounds may be neuroprotective in AD and PD *in vivo*

models and may extend the lifespan through the modulation of critical antioxidant pathways (Crews et al., 2016). *C. zeylanicum* (200 and 400 mg/kg/bw) can provide protection against AD and dementia in the scopolamine-induced memory impairment experimental rat models attributed to a certain reduction in MDA and GSH oxidative stress parameter (Jain et al., 2015).

PPs have been reported to induce the mitogen-activated protein kinase (MAPK) pathway, which stimulates the antioxidant responsive element (ARE)-activated reporter genes and phase II detoxification enzymes (glutathione S-transferase, NAD(P)H-quinone oxido-reductase), that leads to the cell protection and enhances cell survival (Maqbool et al., 2016; Rahimi et al., 2010; Rahman et al., 2006). For instance, Kim and collaborators showed cinnamaldehyde (2 or 6 mg/kg/bw) effectively inhibited age-related protein transcription nuclear factor-kappaB (NF-κB) activation in rats via three signal transduction pathways; NIK/ IKK, ERK, and p38 MAPK. They also concluded that the anti/ pro-inflammatory action of cinnamaldehyde might be obligated to its antioxidant potential and the restoration of redox balance (Kim et al., 2007).

The potential role of PPs in the pathogenesis of AD via the regulation of sirtuin (SIRT) proteins was newly specified. SIRTs are involved in cell survival and often act as neuroprotective (Jayasena et al., 2013). In a study, procyanidin type-A polymers (10 and 20 μg/ml) isolated from an aqueous extract of cinnamon lessened H_2O_2-induced down regulation of the atrophic factor, S100β secretion, through enhanced the expression of SIRT1 in C6 rat glioma cells. This might be contributed to the suppression of the expressions of TNF-α, NF-κB p65, and Bcl-2 family members (Qin et al., 2014a). It has been verified that S100B is associated with the principle mechanisms of neurodegeneration in AD (Petzold et al., 2003). Similarly, different mixture of cinnamon enriched with type A PPs (10 and 20 μg/ml), exhibited significant neuroprotective effects in C6 rat glioma

cells by upregulation of SIRT1, activation of MAPK pathways and suppression of pro-inflammatory cytokines (Qin et al., 2014b).

5.2. Cinnamon and pro-inflammatory function

Researchers illustrated that AD comprises strong interactions with chronic neuroinflammation (Heneka et al., 2015). Pro-inflammatory mediators (chemokines (IL-8, MIP-1a, MCP1, RANTES, eotaxin), interferons (IFN), interleukins (IL-1, IL-2, IL-6), lymphokines and tumor necrosis factors (TNF)), eicosanoids (prostaglandins and leukotrienes) and even ROS compounds have been found to be prominent in higher intensities in the brain of AD patients. Likewise, some of these factors have been monitored along all the stages of disease (Latta et al., 2015).

PPs are well characterized by their pro/ anti-inflammatory functions (Chen et al., 2016; Korkina et al., 2011). PPs modulate the pivotal cellular signaling pathways, predominantly those engage protein NF-κB B and MAPK. It was also proposed that brain-permeable inhibitors of NF-κB signaling have the potential to hinder AD (Hoffmann and Baltimore, 2006; Karunaweera et al., 2015; Rahman et al., 2006). In a regularly basis, NF-κB and its subunits (p65 and/or p50) are maintained in passive forms by IκB family in the cytosol. Upon the stimulation, IκBα is phosphorylated, inactivated and degraded via a polyubiquitination procedure, where NF-κB is translocated to the nuclear and subsequently a cascade of pro-inflammatory factors is incited (Paris et al., 2007). The level of NF-κB increases along aging and increased NF-κB expression results in the up-regulation of β-secretase cleavage and Aβ production (Goyarzu et al., 2003).

PPs affect the NF-κB pathway in a coordinated manner, either through the inhibition of transcription of pro-inflammatory cytokines or by preventing the interaction of NF-κB subunits to the objective DNA. As a result, the transcription of pro-inflammatory

cytokines, the expression of NF-κB downstream pro-inflammatory factors and several enzymes [iNOS and cyclooxygenase (COX-2)] are repressed (Karunaweera et al., 2015; Ruiz and Haller, 2006). Microarray analysis showed young twigs of *C. cassia* inhibited the activation of a number of pro-inflammatory cytokines to suppress the inflammation induced by LPS in the BV2 microglial cells (Hwang *et al.*, 2009). In a study conducted in 2013, the crude extract of *C. cassia* and its constituents contributed to conquer the uncontrolled activation of microglial cells. Both cinnamon extract (50 μg/ml) and cinnamaldehyde (100 μM) reduced the production and expression of nitric oxide (NO), IL-1β, IL-6 and TNFα by inhibiting NF-κB lipopolysaccharide (LPS) induced BV2 microglia cells. Cinnamaldehyde was found as the most potent anti-inflammatory compound, followed by 2-methoxycinnamaldehyde, α-methyl cinnamaldehyde, eugenol and cinnamyl alcohol (Ho et al., 2013).

Earlier, it has been observed that the inhibitory effect of cinnamaldehyde upon TNFα-induced NF-κB activation might be attributed to the pretreatment times in endothelial cells. In a short term, the NF-κB inhibition by cinnamaldehyde was the result of the obstruction of IκBα degradation, whereas, over a long term pretreatments, the inhibitory occurred via the induction of Nrf2-related pathway mainly involved in the regulation of the intracellular thiol redox state (Liao et al., 2008). Trans-cinammaldehyde has also been found to inhibit neuroinflammation via the interruption of NF-κB, besides p53 pathway, by down-regulation of iNOS, COX-2 and TNFα gene expressions in LPS-induced BV2 microglial cells, therefore ameliorated the brain injury (Pyo et al., 2013; Chen et al., 2016). Zhang and his group achieved the same results and proposed this compound mediated MEK1/2-ERK1/2 signaling pathway in LPS-stimulated microglias in mice (Zhang et al., 2016b).

In addition, cinammaldehyde down-regulated the ligand-induced toll-like receptor 4 (TLR4) oligomerization, NF-κB activation and other target genes such as COX-2 and

IFNβ in macrophages (RAW264.7) (Youn et al., 2008). TLR4 has been reported as a mediator of AD and plays a critical role in the normal Aβ clearance (Gambuzza et al., 2014; Marta et al., 2009; Tahara et al., 2006). Another investigation exhibited NaB exerts similar anti-inflammatory effect in murine model of microglia with LPS-induced inflammation. NaB blocked the production of IL-1b and TNF-a, iNOs, and several immunochemicals (CD68, CD11c and CD11b). Inhibition of DNA-binding of NF-κB was the most likely anti-inflammatory mechanism of NaB (Brahmachari et al., 2009). It was suggested that NaB may pass through the BBB, so it could change the neuroimmunology of encephalomyelitis and ameliorated the disease process in multiple sclerosis disease (Pahan, 2011). Figure 2 depicts the effect of cinnamon on pathways that modulate AD prevention or progression.

Jana et al., 2013 proposed cinnamon may pose its neuroprotective action in a direction beyond NF-κB pathway. The authors offered that oral administration of cinnamon powder increased the level of NaB in serum and brain and upregulated the expression of NFs (BDNF and NT-3) within the brain cells and CSN in mice through the activation of protein kinase A (PKA) and cyclic AMP (cAMP) response element binding (CREB) protein. Further, oral feeding of NaB (250 µM) alone, activated the same mechanism and pathway in the CNS of these animals. They concluded that cinnamon and NaB may benefit neurodegenerative disorders via increased production of NFs. NFs belong to a family of small proteins that govern neurogenesis and neuronal function, survival, differentiation or growth. Former studies revealed NFs protect neuronal cells from deprivation processes. Moreover, some NFs are reported to be remarkably suppressed in the brain of AD patients (Peng et al., 2005). Jeon and colleagues demonstrated that a mixture of various neuroprotective compounds, including cinnamic acid, at low concentrations, exhibited synergistically stimulation of brain derived neurotrophic factor (BDNF) in neurological

disease such as AD. This mixture also induced mRNA and protein expression through the phosphorylation of ERK and cAMP- CREB protein and inhibition of iNOS upregulation in cultured rat primary cortical neurons (Jeon et al., 2010). Likewise, cinnamic acid enhanced the BDNF release in cultured rat primary cortical neurons. It is known that eugenol has favorable effects for AD treatment, as it can alleviate Aβ induced neurotoxicity and increase the expression of BDNF gene in the hippocampus (Irie, 2006). Bioactive components of cinnamon *spp*. with neuroprotective activity through different paths are incorporated in Table 3.

6. Effects of cinnamon in other pathophysiological conditions

6.1. *Cinnamon, AD and endothelial functions*

It was put forward that vascular defects, neural and vascular inflammation and brain endothelial dysfunction are frequently diagnosed in AD brain. Aβ peptides are scavenged from the brain through variant mechanisms such as passage to the CSF with subsequent re-absorption into the venous circulation, and direct conduction across the BBB (Zlokovic, 2004). Aβ peptides are transported by receptors for advanced glycation end-products (RAGE) to the perivascular space. Silverberg et al showed that RAGE expression was elevated with age, whereas lipoprotein receptor-related protein 1 (LRP-1) and P-glycoprotein (P-gp) were declined suggesting a potential path for increased Aβ deposition and decreased clearance, respectively (Silverberg et al., 2010). It has also been verified that the BBB endothelium has a potential role in the production of Aβ through proteolytic processing of Aβ precursor protein (Di Marco et al., 2015). However, the extent to which this phenomenon could contribute to the parenchymal accumulation of the peptide and to the neurodegenerative process remains to be established *in vivo*. Normal vascular functionality guarantees a balanced blood flow in the brain. It has been reported that

cerebral blood flow velocity is decreased in AD patients (Ruitenberg et al., 2005). In addition, brain endothelial cells regulate the neuronal environment and any disruption in their function could result in the formation of a toxic neuronal condition in AD brain. Consequently, Aβ deposition happens and in turn Aβ stimulates the release of inflammatory mediators (Grammas, 2011). Toxic Aβ may also affect endothelial cells and cause endothelial-dependent vasoconstriction (Paris et al., 2003). Recently, it was publicized that phytochemical compositions of *C. verum* (3 g of sticks for 5 days) improved the blood circulation and endothelium function, increased cyclic guanosine monophosphate (cGMP) and the mediator of nitric oxide (NO) levels, likewise elevated vascular smooth-muscle relaxation in in patients with type 2 diabetes mellitus (DM) (Azimi et al., 2016).

Yanga and colleagues claimed that cinnamaldehyde acts as a vasorelaxant on isolated rat aortas in an endothelium-dependent manner (Yanaga et al., 2006), although in another study cinnamaldehyde distended vascular smooth muscle in an endothelium independent way. They concluded that the vasodilatory effect of cinnamaldehyde may be associated to both Ca^{2+} influx and Ca^{2+} release (Xue et al., 2011). Cinnamaldehyde prevented the progress of hypertension in both types of diabetes by regulation of vascular contractility, besides affecting on the production and activity of insulin in deficiency situations (El-Bassossy et al., 2011). In addition, cinnamaldehyde attenuated vascular cell adhesion molecule-1 (VCAM-1) and sICAM-1 levels by inhibiting TNFα-induced expression of endothelial factors, also suppressed their transcriptional levels by decreasing (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1) messenger RNA levels (Liao et al., 2008). Wang and colleagues showed cinnamaldehyde devoted a protective effect towards endothelial dysfunction under hyperglycemic conditions and this phenomenon

was mediated by Nrf2 activation and the up-regulation of downstream target proteins (Wang et al., 2015; Wang et al., 2005).

6.2. Cinnamon, AD and diabetes

The probability that patients with type 2 diabetes (DM) ultimately experience AD is estimated to be soaring, that's why a number of references consider AD as a kind of diabetes. The term “type 3 diabetes/ brain diabetes” has been raised to describe AD (Kroner, 2009). Cognitive impairment is known to be one of the dreary consequences of DM. This idea comes from the fact that the imbalanced glucose metabolism damages brain cells, since the glucose level influences their vigorous functions (Strachan et al., 1997). In addition, insulin and insulin signaling mechanisms are imperative for neuronal survival, since the expression of the insulin receptors has been reported to be lowered in AD patients (Dalai et al., 2014; de la Monte and Wands, 2008). A meta-analysis study published in 2010, reported that the obesity and diabetes significantly and independently increased the risk for developing AD (Profenno et al., 2010). In a comparative study of AD patients with non-AD group, 81% of AD patients showed either type 2 diabetes or impaired blood glucose levels (Janson et al., 2004). Aforementioned, cinnamon persuades cellular antioxidant defense mechanisms. Moreover, it is well established oxidative stress plays a major role in both MD and AD. Oxidative stress has also been proven to affect common hallmarks of AD and DM including proteins and nucleic acids destruction as well as cellular glycoxidation and lipid peroxidation (Tabatabaei-Malazy et al., 2015). Cinnamon PPs; catechin, epicatechin and procyanidin B2 showed significant inhibitory effects towards the formation of three typical advanced glycation endproducts (AGEs), which were ascribed to their antioxidant and carbonyl scavenging capacities (Peng et al., 2008; Peng et al., 2010).

Above all, cinnamon and its components possess insulin-like or insulin-potentiating properties. Also, cinnamon is reported to ameliorate insulin function and insulin sensitivity, and modulate glucose uptake and glucose uptake-related genes expression (Couturier et al., 2011; Qin et al., 2010). Insulin resistance is known to be involved in AD pathogenesis and memory impairment. Cinnamon increases the peripheral insulin resistance, but the exact mechanism in the brain cells is not yet recognized. In rat models fed with a diet rich in high fat/ high fructose (HF/HFr) and an aqueous extract of *C. burmannii* (20 g/kg/bw), the behavioral changes and AD related mRNA expression of the brain cells were measured. The lyophilized water extracts of *C. cassia* (2%) decreased TNF-α and iNOS neuroinflammation and enhanced insulin signaling, prevented hippocampal amyloid-β accumulation and deposition, so improved cognitive dysfunction in hippocampal amyloid-β (25–35)-infused AD rats (Park et al., 2016). Cinnamon extract significantly inhibited the aggregation and formation of tau and amyloid precursor proteins, indicating that cinnamon could effectively improve insulin sensitivity (Anderson et al., 2013). In accordance, cinnamon proanthocyanidins were found to inhibit the misfolding of human islet amyloid polypeptide, a proposed causative factor for DM (Jiao et al., 2013). Lu and teammates also verified cinnamon procyanidin oligomers (type A and B) may improve insulin sensitivity (Lu et al., 2011).

7. Cinnamon; bioavailability and clinical application in neurodegenerative disorders

In case of natural compounds, their pharmacokinetics, bioavailability, bioactivity and metabolism within the human body have attained serious concerns as they extensively differ from one compound to another. Their biological profile, availability and absorption rate widely depends on their chemical structures (Singh et al., 2008). This matters more

when it comes to the brain area by means of whether these compounds are capable to reach the brain in adequate quantity and are they still biologically active?

The analytical investigations have indicated that PPs are highly metabolized or eradicated through the digestive system in body, whereas their absorption rate is remarkably low. Cinnamaldehyde naturally exists in trans-cinnamaldehyde form (Zhang et al., 2015) and has shown low bioavailibilty (< 20%) and stability when was fed to rats (50 mg/kg/bw) (Yuan et al., 1992). Contrary, it was exhibited cinnamaldehyde has a half-life of 6.7 h and is stable in rat plasma at room temperature for 24 h after oral administration (Zhao et al., 2014). Even now, it is assumed that cinnamaldehyde is well distributed throughout the body after absorption (Zhu et al., 2017), but its low water solubility may confine its pharmacological effectiveness (Han and Cui, 2012). HPLC analysis exhibited; upon oral administration of *Ramulus cinnamomi* in rats, the metabolism of cinnamaldehyde to cinnamic acid was partially in stomach and small intestine, and almost was completed in liver before it was absorbed into the blood stream. In return, cinnamic acid was absorbed and metabolized into hippuric acid in liver (Chen et al., 2009) To obtain a whole view of pharmacokinetic properties of cinnamaldehyde, an evaluation of methyl cinnamate and cinnamyl alcohol in the plasma seems requisite, because the bioactivity of cinnamaldehyde is mostly depending on the quantity of its metabolites (Zhu et al., 2017). It was shown that a semi-synthetic derivative (2′-Benzoyloxycinnamaldehyde) of cinnamaldehyde is not traceable in the plasma subsequent to either intravenous or oral administrations in rodents, while the other one (2′-hydroxycinnamaldehyde) was detected at a considerable level (Lee et al., 2009a; Lee et al., 2009b). More information and criteria of cinnamaldehyde have been illustrated by Zhu et al., 2017.

It was illuminated that procyanidins (monomers to polymers) might face some limitations regarding absorption or transition along the intestinal tract (Monagas et al., 2010) The

decomposition of these compounds is highly dependent on the pH value of gastric juice and diet intake. Methylated and glucuronidated procyanidins dimers and monomers are their main metabolites found in plasma (Zhang et al., 2016b). Recently, the pharmacokinetic examination of cinnamon bark (1 g/kg/bw) showed following ingestion, various metabolites of epicatechin and procyanidins were detectable in the urine and feces of rats. Further, they found these phenolic metabolites were in contact with the intestinal walls for hours after ingestion, confirming the idea that the metabolism, absorption, conjugation and bioavailability of these compounds might be more than it was supposed (Mateos-Martín et al., 2012). In other hand, the polymeric structures of catechin and epicatechin were not frequently bioavailable as the monomeric forms (Peterson et al., 2009). Today, various formulation strategies such as nanoparticles, lipids carriers, selfemulsifying and solid dispersions are employed to overcome such defects.

Besides the chemical structures, PPs molecular weight, their interactions with BBB and other substrate transporters of the brain blood circulation system, are also considered as determinants factors (Singh et al., 2008). It was evidenced that proanthocyanidins isolated from grapes could pass throughout the BBB (Janle et al., 2007). Furthermore, it has been suggested that brain deposition of PPs is directly affected by the number of dosing rather than a single supplementation (Singh et al., 2008, Ferruzzi et al., 2009).

Together, the bioavailability and brain permeability of cinnamon components are not clarified yet and should be investigated thoroughly. Regarding AD, various studies have reported the favorable metabolic effects of cinnamon and its components or metabolites *in vitro* condition, while only a few were conducted clinically. It has been suggested the long-term *in vivo* experimental designation seems necessary to assess Aβ pathology in AD patients, for the reason that prolonged supplementation of anthocyanin may inhibit Aβ-aggregation *in vivo* models but not *in vitro* cells (Vepsäläinen et al., 2013). The potential

health benefits of cinnamon for free-living humans; clinical trials, animal and *in vitro* studies have been comprehensively reviewed by Gruenwald et al., 2010. Based on their conclusion, the clinical trials on hyperglycemic properties of cinnamon are the most well-documented data of this spice about human health. A different systematic review also concluded that plethora randomized controlled trials in human subjects are needed to confirm the public health implications of cinnamon, since relevant information is sparsely available (Ranasinghe et al., 2013). Yet, the fact that whether cinnamon is able to act as a neuroprotective agent *in vivo* condition remains controversial.

9. Conclusion

Altogether, there is an emerging prerequisite to commence a systematic and comprehensive exploration of different species of the genus cinnamomum regarding their exquisite therapeutic values. Precise and well controlled clinical trials should be constructed to escalate the credibility and safety profiles of various cinnamon *spp*. Interestingly, cinnamon has been profited from the advantages of an extended variety of phytochemicals known as procyanidins, catechins, coumarins, flavonoids, terpenes, minerals and some others. Pharmacokinetic studies of the bioavailability and bioefficacy of bioactive molecules of cinnamon are important concerns. The deficiency of micronutrients or their malabsorption has been correlated with the incidence of dementia or perhaps other neurodegenerative impairments. *In vivo*, cinnamon has shown to lessen oxidative stress and several neuronal inflammations. In AD models, cinnamon has reduced the neurotoxicity of Aβ, inhibited Aβ generation and assemblage, prevented tau aggregation and improved cognitive function. Cinnamon polyphenolics may improve dementia through their hypotensive and vasorelaxant potentials and by attenuating vascular cell adhesion molecules expression within the endothelial cells. Moreover,

cinnamon PPs may practice their neuroprotective potentials by regulating the signal transduction events and modulating of gene expression profiles. As the main bioactive components of cinnamon *spp*. cinnamaldehyde and procyanidins are found to suppress AD, hence interrupt both oxidative and inflammatory cascade of actions in the brain cells. In an optimistic prospect, cinnamon PPs may also be able to induce epigenetic alterations and mediate the expression of genes related to the etiology of AD. Together, cinnamon strongly abrogates neurodegeneration procedure and displays remarkable neuroprotective effects in AD models via the multiple routes.

Conflict of Interest Statement

The authors indicate no conflict of interest with the subject matter of this review.

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10. References

Abraham, K., Wöhrlin, F., Lindtner, O., Heinemeyer, G. & Lampen, A., 2010. Toxicology and risk assessment of coumarin: focus on human data. Molecular nutrition & food research, 54, 228-239.

Ahmad, R.A., Serati-Nouri, H., Majid, F.a.A., Sarmidi, M.R. & Aziz, R.A., 2015. Assessment of Potential Toxicological Effects of Cinnamon Bark Aqueous Extract in Rats. International Journal of Bioscience, Biochemistry and Bioinformatics, 5, 36.

Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A., Khani, M., 2003a. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 74, 863-866.

Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A., Khani, M., 2003b. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther 28, 53-59.

Amadoro, G., Corsetti, V., Ciotti, M., Florenzano, F., Capsoni, S., Amato, G., Calissano, P., 2011. Endogenous Aβ causes cell death via early tau hyperphosphorylation. Neurobiol Aging 32, 969-990.

Anand, P., Singh, B., Singh, N., 2012. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorg Med Chem Lett 20, 1175-1180.

Anderson, R.A., Qin, B., Canini, F., Poulet, L., Roussel, A.M., 2013. Cinnamon counteracts the negative effects of a high fat/high fructose diet on behavior, brain insulin signaling and Alzheimer-associated changes. PloS one 8, e83243.

Anderson, R.A., 2008. Chromium and polyphenols from cinnamon improve insulin sensitivity: Plenary Lecture. Proceedings of the Nutrition Society, 67, 48-53.

Anand, P., Murali, K., Tandon, V., Murthy, P. & Chandra, R., 2010. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chemico-biological interactions, 186, 72-81.

Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T., Hyman, B.T., 1992. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42, 631-631.

Atta-ur-Rahman, Fatima, N., Akhtar, F., Choudhary, M.I., Khalid, A., 2000. New norditerpenoid alkaloids from Aconitum falconeri. J Nat Prod 63, 1393-1395.

Azimi, P., Ghiasvand, R., Feizi, A., Hosseinzadeh, J., Bahreynian, M., Hariri, M., Khosravi-Boroujeni, H., 2016. Effect of cinnamon, cardamom, saffron and ginger consumption on blood pressure and a marker of endothelial function in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. Blood Press 25, 133-140.

Babu, P.S., Prabuseenivasan, S. & Ignacimuthu, S., 2007. Cinnamaldehyde—a potential antidiabetic agent. Phytomedicine, 14, 15-22.

Barceloux, D.G., 2008. Medical toxicology of natural substances: foods, fungi, medicinal herbs, plants, and venomous animals: John Wiley & Sons.

Baselga-Escudero, L., Bladé, C., Ribas Latre, A., Casanova, E., Salvadó, M.J., Arola, L. & Arola -Arnal, A., 2 regulators miR-33 and miR-122 in rats. Molecular nutrition & food research, 56, 1636-1646.

Bekir, J., Mars, M., Souchard, J.P. & Bouajila, J., 2013. Assessment of antioxidant, anti-inflammatory, anti-cholinesterase and cytotoxic activities of pomegranate (Punica granatum) leaves. Food and chemical toxicology, 55, 470-475.

Blevins, S.M., Leyva, M.J., Brown, J., Wright, J., Scofield, R.H., Aston, C.E., 2007. Effect of cinnamon on glucose and lipid levels in Non–insulin-dependent type 2 diabetes. Diabetes care. 30, 2236-2237.

Bradley-Whitman, M., Lovell, M., 2013. Epigenetic changes in the progression of Alzheimer's disease. Mech Ageing Dev 134, 486-495.

Brahmachari, S., Jana, A., Pahan, K., 2009. Sodium benzoate, a metabolite of cinnamon and a food additive, reduces microglial and astroglial inflammatory responses. J Immunol 183, 5917-5927.

Cao, H., Polansky, M.M., Anderson, R.A., 2007. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 459, 214-222.

Carpinella, M.C., Andrione, D.G., Ruiz, G., Palacios, S.M., 2010. Screening for acetylcholinesterase inhibitory activity in plant extracts from Argentina. Phytother Res 24, 259-263.

Cárdenas, A.M., Ardiles, A.O., Barraza, N., Baéz-Matus, X. & Caviedes, P., 2012. Role of tau protein in neuronal damage in Alzheimer's disease and Down syndrome. Archives of medical research, 43, 645-654.

Chanotiya, C., Yadav, A., 2010. Enantioenriched (3S)-(+)-linalool in the leaf oil of Cinnamomum tamala Nees et Eberm. from Kumaon. J Essent Oil Res 22, 593-596.

Chauhan, N.B., 2006. Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. J Ethnopharmacol 108, 385-394.

Chauhan, N.B., 2006. Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. Journal of ethnopharmacology, 108, 385-394.

Chen, P., Sun, J. & Ford, P., 2014a. Differentiation of the four major species of cinnamons (C. burmannii, C. verum, C. cassia, and C. loureiroi) using a flow injection

mass spectrometric (FIMS) fingerprinting method. Journal of agricultural and food chemistry, 62, 2516-2521.

Chen, X., Mukwaya, E., Wong, M.-S. & Zhang, Y., 2014b. A systematic review on biological activities of prenylated flavonoids. Pharmaceutical biology, 52, 655-660.

Chen, Y., Ma, Y. & Ma, W., 2009. Pharmacokinetics and bioavailability of cinnamic acid after oral administration of Ramulus Cinnamomi in rats. European journal of drug metabolism and pharmacokinetics, 34, 51-56.

Chen, Y.-F., Wang, Y.-W., Huang, W.-S., Lee, M.-M., Wood, W.G., Leung, Y.-M., Tsai, H.-Y., 2016. Trans-cinnamaldehyde, an essential oil in cinnamon powder, ameliorates cerebral ischemia-induced brain injury via inhibition of neuroinflammation through attenuation of iNOS, COX-2 expression and NFκ-B signaling pathway. Neuromolecular Med 18, 322-333.

Choi, S.-W., Friso, S., 2010. Epigenetics: a new bridge between nutrition and health. ADV Nute Res 1, 8-16.

Choudhary, M.I., Shahnaz, S., Parveen, S., Khalid, A., Ayatollahi, S.A.M., Parvez, M., 2003. New Triterpenoid Alkaloid Cholinesterase Inhibitors from Buxus h yrcana. J Nat Prod 66, 739-742.

Clapp, P.W., Pawlak, E.A., Lackey, J.T., Keating, J.E., Reeber, S.L., Glish, G.L. & Jaspers, I., 2017. Flavored E-cigarette Liquids and Cinnamaldehyde Impair Respiratory

Innate Immune Cell Function. American Journal of Physiology-Lung Cellular and Molecular Physiology, ajplung. 00452.2016.

Couturier, K., Qin, B., Batandier, C., Awada, M., Hininger-Favier, I., Canini, F., Leverve, X., Roussel, A.M., Anderson, R.A., 2011. Cinnamon increases liver glycogen in an animal model of insulin resistance. Metabolism 60, 1590-1597.

Crews, R., Gomada, Y., Jamison, B., Vattem, D., 2016. Molecular Effects of Cinnamon Bioactive Compounds for Neuroprotection in D. Melanogaster. The FASEB Journal 30, 692.612-692.612.

Dalai, M.K., Bhadra, S., Chaudhary, S.K., Bandyopadhyay, A., Mukherjee, P.K., 2014. Anti-cholinesterase potential of Cinnamomum tamala (Buch.-Ham.) T. Nees & Eberm. leaves. IJTK 13, 691-697.

Davis, J.M., Murphy, E.A., Carmichael, M.D., Davis, B., 2009. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 296, R1071-R1077.

Das, A., Shanker, G., Nath, C., Pal, R., Singh, S. & Singh, H.K., 2002. A comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba: anticholinesterase and cognitive enhancing activities. Pharmacology Biochemistry and Behavior, 73, 893-900.

Devi, L., Alldred, M.J., Ginsberg, S.D. & Ohno, M., 2012. Mechanisms underlying insulin deficiency-induced acceleration of β-amyloidosis in a mouse model of Alzheimer's disease. PLoS One, 7, e32792.

De la Monte, S.M., Wands, J.R., 2008. Alzheimer's disease is type 3 diabetes—evidence reviewed. J Diabetes Sci Technol 2, 1101-1113.

de Oliveira, R.M., Sarkander, J., Kazantsev, A.G., Outeiro, T.F., 2012. SIRT2 as a therapeutic target for age-related disorders. Front Pharmacol 3.

Di Marco, L. Y., Venneri, A., Farkas, E., Evans, P.C., Marzo, A., Frangi, A.F., 2015. Vascular dysfunction in the pathogenesis of Alzheimer's disease—a review of endothelium-mediated mechanisms and ensuing vicious circles. Neurobiol. Dis 82, 593-606.

Dincer, Y., Sezgin, Z., 2014. Medical radiation exposure and human carcinogenesis-genetic and epigenetic mechanisms. Biomed Environ Sci 27, 718-728.

Donley, J., Hurt, W. & Stockert, A., 2016. Effects of cinnamon extract on glycogen synthase kinase 3 phosphorylation of tau. The FASEB Journal, 30, 814.5-814.5.

Drug Interactions with Cinnamon Bark Oral and Warfarin Oral. 2017 a. RxList. Retrieved November 1, 2017 from web site: http://www.rxlist.com/drug-interactions/cinnamon-bark-oral-and-warfarin-oral-interaction.htm

Drug Interactions with Cinnamon Bark Oral and Aspirin Oral. 2017 b. RxList. Retrieved November 1, 2017 from web site: https://www.rxlist.com/drug-interactions/aspirin-oral-and-cinnamon-bark-oral-interaction.htm.

Dementia statistics. Alzheimer's Disease International. 2016. (https://www.alz.co.uk/research/statistics).

Dugoua, J.-J., Seely, D., Perri, D., Cooley, K., Forelli, T., Mills, E. & Koren, G., 2007. From type 2 diabetes to antioxidant activity: a systematic review of the safety and efficacy of common and cassia cinnamon bark This article is one of a selection of papers published in this special issue (part 1 of 2) on the Safety and Efficacy of Natural Health Products. Canadian journal of physiology and pharmacology, 85, 837-847.

Gambuzza, M.E., Sofo, V., M Salmeri, F., Soraci, L., Marino, S., Bramanti, P., 2014. Toll-like receptors in Alzheimer's disease: a therapeutic perspective. CNS Neurol Disord Drug Targets 13, 1542-1558.

El-Bassossy, H.M., Fahmy, A., Badawy, D., 2011. Cinnamaldehyde protects from the hypertension associated with diabetes. Food Chem Toxicol 49, 3007-3012.

El Mohsen, M.M.A., Kuhnle, G., Rechner, A.R., Schroeter, H., Rose, S., Jenner, P. & Rice-Evans, C.A., 2002. Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. Free Radical Biology and Medicine, 33, 1693-1702.

Emerit, J., Edeas, M., Bricaire, F., 2004. Neurodegenerative diseases and oxidative stress. Biomed Pharmacother 58, 39-46.

European Parliament and Council Directive No. 1334/2008 on the flavourings and certain food ingredients with flavouring properties for use in and on food and amending Council Regulation (EEC) No. 1601/91, Regulations (EC) No. 2232/96 and (EC) No. 110/2008 and Directive 2000/13/EC, Official Journal of the European Communities, vol. L354/34, pp. 14–15, 2008.

Fani, A., Malekirad, A.A., Allahnazem, H., Rahzani, K., Ranjbar, A., Vosoughghanbari, S., Abdollahi, M., 2008. On the benefit of cinnamomum zeylanicum for radiology unit staff. Int J Med Sci 8, 384-389.

Fazlullah Khan , K.N., Faheem Maqbool , Fatima Ismail Hassan , Mohammad Abdollahi , Kalyan C. Nagulapalli Venkata, Seyed Mohammad Nabavi & Bishayee, A., 2016. Molecular Targets Underlying the Anticancer Effects of Quercetin: An Update. Nutrients, 8, 19.

Fernández-Bachiller, M.I., Pérez, C., Campillo, N.E., Páez, J.A., González-Muñoz, G.C., Usan, P., García-Palomero, E., López, M.G., Villarroya, M., García, A.G., 2009. Tacrine–melatonin hybrids as multifunctional agents for Alzheimer's disease, with cholinergic, antioxidant, and neuroprotective properties. Chem Med Chem 4, 828-841.

Ferruzzi, M.G., Lobo, J.K., Janle, E.M., Cooper, B., Simon, J.E., Wu, Q.L., Welch, C., Ho, L., Weaver, C., Pasinetti, G.M., 2009. Bioavailability of gallic acid and catechins

from grape seed polyphenol extract is improved by repeated dosing in rats: implications for treatment in Alzheimer's disease. J Alzheimers Dis, 18**,** 113-124.

Frydman-Marom, A., Levin, A., Farfara, D., Benromano, T., Scherzer-Attali, R., Peled, S., Vassar, R., Segal, D., Gazit, E., Frenkel, D., 2011. Orally administrated cinnamon extract reduces β-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models. PloS one 6, e16564.

Fujiwara, H., Iwasaki, K., Furukawa, K., Seki, T., He, M., Maruyama, M., Tomita, N., Kudo, Y., Higuchi, M., Saido, T.C., 2006. Uncaria rhynchophylla, a Chinese medicinal herb, has potent antiaggregation effects on Alzheimer's β-amyloid proteins. J Neurosci Res 84, 427-433.

Fujiwara, H., Tabuchi, M., Yamaguchi, T., Iwasaki, K., Furukawa, K., Sekiguchi, K., Ikarashi, Y., Kudo, Y., Higuchi, M., Saido, T.C., 2009. A traditional medicinal herb Paeonia suffruticosa and its active constituent 1, 2, 3, 4, 6-penta-O-galloyl-β-d-glucopyranose have potent anti-aggregation effects on Alzheimer's amyloid β proteins in vitro and in vivo. J Neurochem 109, 1648-1657.

Gende, L.B., Floris, I., Fritz, R., Eguaras, M.J., 2008. Antimicrobial activity of cinnamon (Cinnamomum zeylanicum) essential oil and its main components against Paenibacillus larvae from Argentine. Bull. Insectology 61, 1.

George, R.C., Lew, J., Graves, D.J., 2013. Interaction of cinnamaldehyde and epicatechin with tau: implications of beneficial effects in modulating Alzheimer's disease pathogenesis. J Alzheimers Dis 36, 21-40.

Goyarzu, P., Lau, F., Kaufmann, J., Jennings, R., Taglialatela, G., Joseph, J., Shukitt-Hale, B., Malin, D., 2003. age-related increase in brain NF-B is attenuated by blueberry-enriched antioxidant diet. Society for Neuroscience, Washington DC.

Gruenwald, J., Freder, J. & Armbruester, N., 2010. Cinnamon and health. Critical reviews in food science and nutrition, 50, 822-834.

Grammas, P., 2011. Neurovascular dysfunction, inflammation and endothelial activation: implications for the pathogenesis of Alzheimer's disease. J Neuroinflammation 8, 26.

Han, C. & Cui, B., 2012. Improvement of the bioavailability and glycaemic metabolism of cinnamon oil in rats by liquid loadable tablets. The Scientific World Journal, 2012.

Hartmann, K. & Hunzelmann, N., 2004. Allergic contact dermatitis from cinnamon as an odour-neutralizing agent in shoe insoles. Contact Dermatitis, 50, 253-254.

Haass, C., Selkoe, D.J., 2007. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 8, 101-112.

Hasani-Ranjbar, S., Nayebi, N., Moradi, L., Mehri, A., Larijani, B., Abdollahi, M., 2010. The efficacy and safety of herbal medicines used in the treatment of hyperlipidemia; a systematic review. Curr Pharm Des 16, 2935-2947.

Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G.E., Brosseron, F., Feinstein, D.L., Jacobs, A.H., Wyss-Coray, T., Vitorica, J., Ransohoff, R.M., 2015. Neuroinflammation in Alzheimer's disease. Lancet Neurol 14, 388-405.

Ho, S.-C., Chang, K.-S., Chang, P.-W., 2013. Inhibition of neuroinflammation by cinnamon and its main components. Food chem 138, 2275-2282.

Hodjat, M., Rahmani, S., Khan, F., Niaz, K., Navaei-Nigjeh, M., Mohammadi, N.S., Abdollahi, M., 2017. Environmental toxicants, incidence of degenerative diseases, and therapies from the epigenetic point of view. Arch Toxicol 91, 2577-2597.

Hoffmann, A., Baltimore, D., 2006. Circuitry of nuclear factor κB signaling. Immunol Rev 210, 171-186.

Hwa, J.S., Jin, Y.C., Lee, Y.S., Ko, Y.S., Kim, Y.M., Shi, L.Y., Kim, H.J., Lee, J.H., Ngoc, T.M., Bae, K.H., 2012. 2-methoxycinnamaldehyde from Cinnamomum cassia reduces rat myocardial ischemia and reperfusion injury in vivo due to HO-1 induction. J Ethnopharmacol 139, 605-615.

Hwang, S.-H., Choi, Y.G., Jeong, M.-Y., Hong, Y.-M., Lee, J.-H. & Lim, S., 2009. Microarray analysis of gene expression profile by treatment of Cinnamomi Ramulus in lipopolysaccharide-stimulated BV-2 cells. Gene, 443, 83-90.

Ibrahim, J.E., Anderson, L.J., Macphail, A., Lovell, J.J., Davis, M.-C. & Winbolt, M., 2017. Chronic disease self-management support for persons with dementia, in a clinical setting. Journal of multidisciplinary healthcare, 10, 49.

Ingkaninan, K., Temkitthawon, P., Chuenchom, K., Yuyaem, T. & Thongnoi, W., 2003. Screening for acetylcholinesterase inhibitory activity in plants used in Thai traditional rejuvenating and neurotonic remedies. Journal of Ethnopharmacology, 89, 261-264.

Irie, Y., 2006. Effects of eugenol on the central nervous system: its possible application to treatment of alzheimer's disease, depression, and parkinson's disease. Curr Bioact Compd 2, 57-66.

Ittner, L.M., Götz, J., 2011. Amyloid-β and tau—a toxic pas de deux in Alzheimer's disease. Nature Rev Neurosci 12, 67-72.

Iuvone, T., De Filippis, D., Esposito, G., D'Amico, A., Izzo, A.A., 2006. The spice sage and its active ingredient rosmarinic acid protect PC12 cells from amyloid-β peptide-induced neurotoxicity. J Pharm Exp Ther 317, 1143-1149.

Jain, S., Sangma, T., Shukla, S.K., Mediratta, P.K., 2015. Effect of Cinnamomum zeylanicum extract on scopolamine-induced cognitive impairment and oxidative stress in rats. Nutr Neurosci 18, 210-216.

Jana, A., Modi, K.K., Roy, A., Anderson, J.A., Van Breemen, R.B., Pahan, K., 2013. Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate:

therapeutic implications for neurodegenerative disorders. J Neuroimmune Pharmacol 8, 739.

Janle, E.M., Lila, M.A., Wood, L., Higgins, A., Yousef, G.G., Rogers, R.B., Kim, H., Jackson, G., Weaver, C.M., 2007. Kinetics and tissue distribution on 14C-labeled grape polyphenol fractions. FASEB 21, 837-11.

Janson, J., Laedtke, T., Parisi, J.E., O'brien, P., Petersen, R.C. & Butler, P.C., 2004. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes, 53, 474-481.

Jayaprakasha, G., Rao, L.J.M., 2011. Chemistry, biogenesis, and biological activities of Cinnamomum zeylanicum. Crit Rev Food Sci Nutr 51, 547-562.

Jayasena, T., Poljak, A., Smythe, G., Braidy, N., Muench, G., Sachdev, P., 2013. The role of polyphenols in the modulation of sirtuins and other pathways involved in Alzheimer's disease. Ageing Res Rev 12, 867-883.

Jeon, S.-J., Bak, H.-R., Seo, J.-E., Kwon, K.-J., Kang, Y.-S., Kim, H.-J., Cheong, J.-H., Ryu, J.-H., Ko, K.-H., Shin, C.-Y., 2010. Synergistic increase of BDNF release from rat primary cortical neuron by combination of several medicinal plant-derived compounds. Biomol Ther 18, 39-47.

Jeong, E.J., Ma, C.J., Lee, K.Y., Kim, S.H., Sung, S.H., Kim, Y.C., 2009. KD-501, a standardized extract of Scrophularia buergeriana has both cognitive-enhancing and antioxidant activities in mice given scopolamine. J Ethnopharmacol 121, 98-105.

Jiao, L., Zhang, X., Huang, L., Gong, H., Cheng, B., Sun, Y., Li, Y., Liu, Q., Zheng, L., Huang, K., 2013. Proanthocyanidins are the major anti-diabetic components of cinnamon water extract. Food Chem Toxicol 56, 398-405.

Jones, J.R., Lebar, M.D., Jinwal, U.K., Abisambra, J.F., Koren III, J., Blair, L., O'Leary, J.C., Davey, Z., Trotter, J., Johnson, A.G., 2010. The diarylheptanoid (+)-a R, 11 S-myricanol and two flavones from bayberry (Myrica cerifera) destabilize the microtubule-associated protein Tau. J Nat Prod 74, 38-44.

Kalauni, S.K., Choudhary, M.I., Shaheen, F., Manandhar, M.D., Atta-ur-Rahman, Gewali, M.B., Khalid, A., 2001. Steroidal Alkaloids from the Leaves of Sarcococca c oriacea of Nepalese Origin. J Nat Prod 64, 842-844.

Kamath, J.V., Rana, A. & Roy Chowdhury, A., 2003. Pro -healing effe Cinnamomum zeylanicum bark. Phytotherapy Research, 17, 970-972.

Kang, Y.J., Seo, D.G., Park, S.g., 2016. Phenylpropanoids from Cinnamon bark reduced β-amyloid production by the inhibition of β- secretase in CHO cells stably expressing amyloid precursor protein, Nutr Res doi: 10.1016/j.nutres.2016.10.002.

Karunaweera, N., Raju, R., Gyengesi, E., Münch, G., 2015. Plant polyphenols as inhibitors of NF-κB induced cytokine production—a potential anti-inflammatory treatment for Alzheimer's disease? Front Mol Neurosci 8.

Khan, F., Niaz, K., Maqbool, F., Ismail Hassan, F., Abdollahi, M., Nagulapalli Venkata, K.C., Nabavi, S.M., Bishayee, A., 2016. Molecular targets underlying the anticancer effects of quercetin: an update. Nutrients 8, 529.

Khasnavis, S., Pahan, K., 2012. Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective Parkinson disease protein DJ-1 in astrocytes and neurons. J. Neuroimmune Pharmacol 7, 424-435.

Kim, D.H., Kim, C.H., Kim, M.-S., Kim, J.Y., Jung, K.J., Chung, J.H., An, W.G., Lee, J.W., Yu, B.P., Chung, H.Y., 2007. Suppression of age-related inflammatory NF-κB activation by cinnamaldehyde. Biogerontology 8, 545-554.

Kim, J.K., Bae, H., Kim, M.-J., Choi, S.J., Cho, H.Y., Hwang, H.-J., Kim, Y.J., Lim, S.T., Kim, E.K. & Kim, H.K., 2009. Inhibitory effect of Poncirus trifoliate on acetylcholinesterase and attenuating activity against trimethyltin-induced learning and memory impairment. Bioscience, biotechnology, and biochemistry, 73, 1105-1112.

Kim, S.R., Hwang, S.Y., Jang, Y.P., Park, M.J., Markelonis, G.J., Oh, T.H., Kim, Y.C., 1999. Protopine from Corydalis ternata has anticholinesterase and antiamnesic activities. Planta Med 65, 218-221.

Kim, Y.-H., Lee, D.-H., Jeong, J.-H., Guo, Z.S., Lee, Y.J., 2008. Quercetin augments TRAIL-induced apoptotic death: involvement of the ERK signal transduction pathway. Biochem Pharmacol 75, 1946-1958.

Koppikar, S.J., Choudhari, A.S., Suryavanshi, S.A., Kumari, S., Chattopadhyay, S., Kaul-Ghanekar, R., 2010. Aqueous cinnamon extract (ACE-c) from the bark of Cinnamomum cassia causes apoptosis in human cervical cancer cell line (SiHa) through loss of mitochondrial membrane potential. BMC cancer 10, 210.

Korkina, L., Kostyuk, V., De Luca, C., Pastore, S., 2011. Plant phenylpropanoids as emerging anti-inflammatory agents. Mini Rev Med Chem 11, 823-835.

Konrath, E.L., Ortega, M.G., De Loreto Bordignon, S., Apel, M.A., Henriques, A.T. & Cabrera, J.L., 2013. Alkaloid profiling and anticholinesterase activity of South American Lycopodiaceae species. Journal of enzyme inhibition and medicinal chemistry, 28, 218-222.

Kroner, Z., 2009. The relationship between Alzheimer's disease and diabetes: Type 3 diabetes? Alternative Medicine Review, 14, 373.

Kumar, S., Harris, R.J., Seal, C.J. & Okello, E.J., 2012. An aqueous extract of Withania somnifera root inhibits amyloid β fibril formation in vitro. Phytotherapy Research, 26, 113-117.

LaFerla, F.M., Green, K.N., Oddo, S., 2007. Intracellular amyloid-β in Alzheimer's disease. Nature Rev Neurosci 8, 499-509.

Latta, C.H., Brothers, H.M., Wilcock, D.M., 2015. Neuroinflammation in Alzheimer's disease; A source of heterogeneity and target for personalized therapy. J Neurosci 302, 103-111.

Lee, K., Kiho Lee, Kwon, B.M., Kim, K., Ryu, J., Oh, S.J., Lee, K.S., Kwon, M.G., Park, S.K., Kang, J.S., Lee, C.W., Kim, H.M., 2009a. Plasma pharmacokinetics and metabolism of the antitumour drug candidate 2′-benzoyloxycinnamaldehyde in rats. Xenobiotica 39, 255-265.

Lee, K., Park, S.K., Kwon, B.M., Kim, K., Yu, H.E., Ryu, J., Oh, S.J., Lee, K.S., Kang, J.S., Lee, C.W., Kwon, M.G., Kim, H.M., 2009b. Transport and metabolism of the antitumour drug candidate 2′-benzoyloxycinnamaldehyde in Caco-2 cells. Xenobiotica 39, 881-888.

Lee, S.-C., Xu, W.-X., Lin, L.-Y., Yang, J.-J., Liu, C.-T., 2013. Chemical composition and hypoglycemic and pancreas-protective effect of leaf essential oil from indigenous cinnamon (Cinnamomum osmophloeum Kanehira). J Agric Food Chem 61, 4905-4913.

Lee, Y.K., Yuk, D.Y., Kim, T.I., Kim, Y.H., Kim, K.T., Kim, K.H., Lee, B.J., Nam, S.-Y., Hong, J.T., 2009c. Protective effect of the ethanol extract of Magnolia officinalis and 4-O-methylhonokiol on scopolamine-induced memory impairment and the inhibition of acetylcholinesterase activity. J Nat Med 63, 274-282.

Lesné, S., Koh, M.T., Kotilinek, L., Kayed, R., Glabe, C.G., Yang, A., Gallagher, M., Ashe, K.H., 2006. A specific amyloid-β protein assembly in the brain impairs memory. Nature 440, 352-357.

Li, L., Liu, J., Yan, X., Qin, K., Shi, M., Lin, T., Zhu, Y., Kang, T., Zhao, G., 2011. Protective effects of ginsenoside Rd against okadaic acid-induced neurotoxicity in vivo and in vitro. Journal of Ethnopharmacol 138, 135-141.

Li, H., Wu, X., Wu, Q., Gong, D., Shi, M., Guan, L., Zhang, J., Liu, J., Yuan, B. & Han, G., 2014. Green tea polyphenols protect against okadaic acid-induced acute learning and memory impairments in rats. Nutrition, 30, 337-342.

Li, J., Liu, T., Wang, L., Guo, X., Xu, T., Wu, L., Qin, L. & Sun, W., 2012. Antihyperglycemic and antihyperlipidemic action of cinnamaldehyde in C57BLKS/J db/db mice. Journal of Traditional Chinese Medicine, 32, 446-452.

Lin, L.-C., Wang, M.-N., Tseng, T.-Y., Sung, J.-S. & Tsai, T.-H., 2007. Pharmacokinetics of (−)-epigallocatechin-3-gallate in conscious and freely moving rats and its brain regional distribution. Journal of agricultural and food chemistry, 55, 1517-1524.

Liao, B.-C., Hsieh, C.-W., Liu, Y.-C., Tzeng, T.-T., Sun, Y.-W., Wung, B.-S., 2008. Cinnamaldehyde inhibits the tumor necrosis factor-α-induced expression of cell adhesion molecules in endothelial cells by suppressing NF-κB activation: Effects upon IκB and Nrf2. Toxicol Appl Pharmacol 229, 161-171.

Lin, C.C., Wu, S.J., Chang, C.H., Ng, L.T., 2003. Antioxidant activity of Cinnamomum cassia. Phytother Res 17, 726-730.

Link, A., Balaguer, F., Goel, A., 2010. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. Biochem Pharmacol 80, 1771-1792.

Liu, H., Zhao, M., Yang, S., Gong, D.-R., Chen, D.-Z., Du, D.-Y., 2015. (2R, 3S)-Pinobanksin-3-cinnamate improves cognition and reduces oxidative stress in rats with vascular dementia. J Nat Med 69, 358-365.

Llibre-Rodríguez, J.D.J., Valhuerdi-Cepero, A., López-Medina, A.M., Noriega-Fernández, L., Porto-Álvarez, R., Guerra-Hernández, M.A., Bosch-Bayard, R.I., Zayas-Llerena, T., Hernandez-Ulloa, E. & Rodríguez-Blanco, A.L., 2017. Cuba's Aging and Alzheimer Longitudinal Study. MEDICC review, 19, 31-35.

Loscalzo, J., Handy, D.E., 2014. Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series). Pulm Circ 4, 169-174.

Manach, C., Williamson, G., Morand, C., Scalbert, A., Remesy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 81, 230S-242S.

Madhavadas, S. & Subramanian, S., 2016. Cognition enhancing effect of the aqueous extract of Cinnamomum zeylanicum on non-transgenic Alzheimer's disease rat model: Biochemical, histological, and behavioural studies. Nutritional neuroscience, 1-12.

Manach, C., Williamson, G., Morand, C., Scalbert, A. & Rémésy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American journal of clinical nutrition, 81, 230S-242S.

Mani, V., Parle, M., Ramasamy, K., Majeed, A., Bakar, A., 2011. Reversal of memory deficits by Coriandrum sativum leaves in mice. J Sci Food Agric 91, 186-192.

Maqbool, F., Mostafalou, S., Bahadar, H., Abdollahi, M., 2016. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. Life sciences 145, 265-273.

Marta, M., Meier, U.C., Lobell, A., 2009. Regulation of autoimmune encephalomyelitis by toll-like receptors. Autoimmun Rev 8, 506-509.

Mattson, M.P., 2000. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol 1, 120-130.

Mateos-Martín, M.L., Pérez -Jiménez, J., urinary and fecal proanthocyanidin metabolites from common cinnamon (Cinnamomum zeylanicum L.) in rats. Molecular nutrition & food research, 56, 671-675.

Ming, D.S., López, A., Hillhouse, B.J., French, C.J., Hudson, J.B., Towers, G.N., 2002. Bioactive Constituents from Iryanthera m egistophylla. J Nat Prod 65, 1412-1416.

Modi, K.K., Rangasamy, S.B., Dasarathi, S., Roy, A., Pahan, K., 2016. Cinnamon Converts Poor Learning Mice to Good Learners: Implications for Memory Improvement. J Neuroimmune Pharmacol 11, 693-707.

Moselhy, S.S., Ali, H.K., 2009. Hepatoprotective effect of cinnamon extracts against carbon tetrachloride induced oxidative stress and liver injury in rats. J Biol Res 42, 93-98.

Modi, K.K., Rangasamy, S.B., Dasarathi, S., Roy, A. & Pahan, K., 2016. Cinnamon Converts Poor Learning Mice to Good Learners: Implications for Memory Improvement. Journal of neuroimmune pharmacology, 11, 693-707.

Monagas, M., Urpi-Sarda, M., Sánchez-Patán, F., Llorach, R., Garrido, I., Gómez-Cordovés, C., Andres-Lacueva, C. & Bartolomé, B., 2010. Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites. Food & function, 1, 233-253.

Morris, M., Maeda, S., Vossel, K. & Mucke, L., 2011. The many faces of tau. Neuron, 70, 410-426.

Mukherjee, P.K., Kumar, V., Mal, M. & Houghton, P.J., 2007. Acetylcholinesterase inhibitors from plants. Phytomedicine, 14, 289-300.

Mukherjee, P.K., Kumar, V., Mal, M., Houghton, P.J., 2007. Acetylcholinesterase inhibitors from plants. Phytomedicine 14, 289-300.

Oboh, G., Ademiluyi, A.O., Akinyemi, A.J., 2012. Inhibition of acetylcholinesterase activities and some pro-oxidant induced lipid peroxidation in rat brain by two varieties of ginger (Zingiber officinale). Exp Toxicol Pathol 64, 315-319.

Ohtsuki, K., Miyai, S., Yamaguchi, A., Morikawa, K., Okano, T., 2012. Biochemical characterization of novel lignans isolated from the wood of Taxus yunnanensis as effective stimulators for glycogen synthase kinase-3β and the phosphorylation of basic brain proteins by the kinase in vitro. Biol Pharm Bull 35, 385-393.

Ooi, L.S., Li, Y., Kam, S.-L., Wang, H., Wong, E.Y., Ooi, V.E., 2006. Antimicrobial activities of cinnamon oil and cinnamaldehyde from the Chinese medicinal herb Cinnamomum cassia Blume. Am J Chin Med 34, 511-522.

Okello, E.J., Savelev, S.U. & Perry, E.K., 2004. In vitro anti -sβcretase and dual anti-cholinesterase activities of Camellia sinensis L.(tea) relevant to treatment of dementia. Phytotherapy Research, 18, 624-627.

Ono, K., Hasegawa, K., Naiki, H. & Yamada, M., 2004. Curcumin has potent anti-amyloidogenic effects for Alzheimer's β -amyloid fibri
research, 75, 742-750.

Orhan, I., Aslan, M., 2009. Appraisal of scopolamine-induced antiamnesic effect in mice and in vitro antiacetylcholinesterase and antioxidant activities of some traditionally used Lamiaceae plants. Journal of Ethnopharmacol 122, 327-332.

Pahan, K., 2011. Immunomodulation of experimental allergic encephalomyelitis by cinnamon metabolite sodium benzoate. Immunopharm. Immunot 33, 586-593.

Panickar, K., Polansky, M., Graves, D., Urban, J., Anderson, R., 2012. A procyanidin type A trimer from cinnamon extract attenuates glial cell swelling and the reduction in glutamate uptake following ischemia-like injury in vitro. Neuroscience 202, 87-98.

Panickar, K.S., Polansky, M.M., Anderson, R.A., 2009. Cinnamon polyphenols attenuate cell swelling and mitochondrial dysfunction following oxygen-glucose deprivation in glial cells. Exp Neurol 216, 420-427.

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

Park, H.R., Lee, H., Park, H., Cho, W.-K., Ma, J.Y., 2016a. Fermented sipjeondaebo-tang alleviates memory deficits and loss of hippocampal neurogenesis in scopolamine-induced amnesia in mice. Sci Rep 6.

Park, I.-K., 2014. Fumigant toxicity of Oriental sweetgum (Liquidambar orientalis) and valerian (Valeriana wallichii) essential oils and their components, including their acetylcholinesterase inhibitory activity, against Japanese termites (Reticulitermes speratus). Molecules 19, 12547-12558.

Park, S.-Y., Kim, H.-S., Cho, E.-K., Kwon, B.-Y., Phark, S., Hwang, K.-W. & Sul, D., 2008. Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation. Food and Chemical Toxicology, 46, 2881-2887.

Paris, D., Humphrey, J., Quadros, A., Patel, N., Crescentini, R., Crawford, F., Mullan, M., 2003. Vasoactive effects of A β in isolated human cerebrovessels and in a transgenic mouse model of Alzheimer's disease: role of inflammation. Neurol Res 25, 642-651.

Paris, D., Patel, N., Quadros, A., Linan, M., Bakshi, P., Ait-Ghezala, G. & Mullan, M., 2007. Inhibition of Aβ production by NF-κB inhibitors. Neuroscience letters, 415, 11-16.

Peng, S., Wuu, J., Mufson, E.J., Fahnestock, M., 2005. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem 93, 1412-1421.

Peng, X., Cheng, K.-W., Ma, J., Chen, B., Ho, C.-T., Lo, C., Chen, F., Wang, M., 2008. Cinnamon bark proanthocyanidins as reactive carbonyl scavengers to prevent the formation of advanced glycation endproducts. J Sci Food Agric 56, 1907-1911.

Peng, X., Ma, J., Chao, J., Sun, Z., Chang, R.C.-C., Tse, I., Li, E.T., Chen, F., Wang, M., 2010. Beneficial effects of cinnamon proanthocyanidins on the formation of specific advanced glycation endproducts and methylglyoxal-induced impairment on glucose consumption. J Sci Food Agric 58, 6692-6696.

Peterson, D.W., George, R.C., Scaramozzino, F., LaPointe, N.E., Anderson, R.A., Graves, D.J., Lew, J., 2009. Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease in vitro. J Alzheimers Dis 17, 585-597.

Pereira, D.M., Ferreres, F., Oliveira, J.M., Gaspar, L., Faria, J., Valentão, P., Sottomayor, M. & Andrade, P.B., 2010. Pharmacological effects of Catharanthus roseus root alkaloids in acetylcholinesterase inhibition and cholinergic neurotransmission. Phytomedicine, 17, 646-652.

Petzold, A., Jenkins, R., Watt, H., Green, A., Thompson, E., Keir, G., Fox, N., Rossor, M., 2003. Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease. Neurosci Lett 336, 167-170.

Profenno, L.A., Porsteinsson, A.P., Faraone, S.V., 2010. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 67, 505-512.

Pyo, J.-H., Jeong, Y.-K., Yeo, S., Lee, J.-H., Jeong, M.-Y., Kim, S.-H., Choi, Y.-G., Lim, S., 2013. Neuroprotective effect of trans-cinnamaldehyde on the 6-hydroxydopamine-induced dopaminergic injury. Biol Pharm Bull 36, 1928-1935.

Qadir, M.M.F., Bhatti, A., Ashraf, M.U., Sandhu, M.A., Anjum, S. & John, P., 2017. Immunomodulatory and therapeutic role of Cinnamomum verum extracts in collagen-induced arthritic BALB/c mice. Inflammopharmacology, 1-14.

Qin, B., Panickar, K.S., Anderson, R.A., 2010. Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. J Diabetes Sci Technol 4, 685-693.

Qin, B., Panickar, K.S., Anderson, R.A., 2014a. Cinnamon polyphenols attenuate the hydrogen peroxide-induced down regulation of S100β secretion by regulating sirtuin 1 in C6 rat glioma cells. Life sciences 102, 72-79.

Qin, B., Panickar, K.S., Anderson, R.A., 2014b. Cinnamon polyphenols regulate S100β, sirtuins, and neuroactive proteins in rat C6 glioma cells. Nutr J 30, 210-217.

Rahimi, R., Ghiasi, S., Azimi, H., Fakhari, S., Abdollahi, M., 2010. A review of the herbal phosphodiesterase inhibitors; future perspective of new drugs. Cytokine 49, 123-129.

Rahman, I., Biswas, S.K., Kirkham, P.A., 2006. Regulation of inflammation and redox signaling by dietary polyphenols. Biochem Pharmacol 72, 1439-1452.

Ranasinghe, P., Pigera, S., Premakumara, G.A.S., Galappaththy, P., Constantine, G.R., Katulanda, P., 2013. Medicinal properties of 'true' cinnamon (Cinnamomum zeylanicum): a systematic review. BMC Complement Altern Med 13, 275.

Ranasinghe, P., Jayawardana, R., Galappaththy, P., Constantine, G., De Vas Gunawardana, N. & Katulanda, P., 2012. Efficacy and safety of 'true'cinnamon

(Cinnamomum zeylanicum) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. Diabetic medicine, 29, 1480-1492.

Ranjbar, A., Ghaseminejhad, S., Takalu, H., Baiaty, A., Rahimi, F., Abdollahi, M., 2007. Anti oxidative stress potential of cinnamon (cinnamomum zeylanicum) in operating room personnel; a before/after cross sectional clinical trial. Int J Pharmacol 3, 482-486.

Rao, P.V., Gan, S.H., 2014. Cinnamon: a multifaceted medicinal plant. Evid Based Complement Alternat Med 2014.

Rashidi, M., Malekirad, A.A., Abdollahi, M., Habibollahi, S., Dolatyari, N., Narimani, M., 2014. The effect of tea-cinnamon and Melissa officinalis L. aqueous extraction, on neuropsychology distress, biochemical and oxidative stress biomarkers in glass production workers. Health 6, 2592.

Regulation, E., 2008. No. 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No. 1601/91, Regulations (EC) No. 2232/96 and (EC) No. 110/2008 and Directive 2000/13/EC. Official Journal of the European Communities, 34-50.

Roberson, E.D., Scearce-Levie, K., Palop, J.J., Yan, F., Cheng, I.H., Wu, T., Gerstein, H., Yu, G.-Q., Mucke, L., 2007. Reducing endogenous tau ameliorates amyloid ß-induced deficits in an Alzheimer's disease mouse model. Science 316, 750-754.

Robert, V., 2004. BACE1: The beta-Secretase Enzyme in Alzheimer's Disease. J Mol Neurosci 23, 1-2.

Rosenwald, A., Wright, G., Chan, W.C., Connors, J.M., Campo, E., Fisher, R.I., Gascoyne, R.D., Muller-Hermelink, H.K., Smeland, E.B., Giltnane, J.M., 2002. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346, 1937-1947.

Roussel, A.-M., Hininger, I., Benaraba, R., Ziegenfuss, T.N., Anderson, R.A., 2009. Antioxidant effects of a cinnamon extract in people with impaired fasting glucose that are overweight or obese. J Am Coll Nutr 28, 16-21.

Ruitenberg, A., den Heijer, T., Bakker, S.L., van Swieten, J.C., Koudstaal, P.J., Hofman, A., Breteler, M., 2005. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol 57, 789-794.

Ruiz, P.A., Haller, D., 2006. Functional diversity of flavonoids in the inhibition of the proinflammatory NF-κB, IRF, and Akt signaling pathways in murine intestinal epithelial cells. J Nutr 136, 664-671.

Saeidnia, S., Abdollahi, M., 2013. Toxicological and pharmacological concerns on oxidative stress and related diseases. Toxicol Appl Pharmacol 273, 442-455.

Schaffer, S. & Halliwell, B., 2012. Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations. Genes & nutrition, 7, 99-109.

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the European Commission on Coumarin in flavourings and other food ingredients with flavouring properties. The EFSA Journal (2008) 793, 1-15.

Shankar, G.M., Li, S., Mehta, T.H., Garcia-Munoz, A., Shepardson, N.E., Smith, I., Brett, F.M., Farrell, M.A., Rowan, M.J., Lemere, C.A., 2008. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 14, 837-842.

Shi, L.-L., Yang, W.-N., Chen, X.-L., Zhang, J.-S., Yang, P.-B., Hu, X.-D., Han, H., Qian, Y.-H., Liu, Y., 2012. The protective effects of tanshinone IIA on neurotoxicity induced by β-amyloid protein through calpain and the p35/Cdk5 pathway in primary cortical neurons. Neurochem Int 61, 227-235.

Shoval, H., Weiner, L., Gazit, E., Levy, M., Pinchuk, I., Lichtenberg, D., 2008. Polyphenol-induced dissociation of various amyloid fibrils results in a methionine-independent formation of ROS. Biochim. Biophys. Acta, Proteins Proteomics 1784, 1570-1577.

Singh, M., Arseneault, M., Sanderson, T., Murthy, V., Ramassamy, C., 2008. Challenges for Research on Polyphenols from Foods in Alzheimer's Disease: Bioavailability, Metabolism, and Cellular and Molecular Mechanisms. J Agric Food Chem 56, 4855-4873.

Singh, N., Pandey, B., Verma, P., 2011. An overview of phytotherapeutic approach in prevention and treatment of Alzheimer's syndrome & dementia. Int. J. Pharm. Sci. Drug Res 3, 162-172.

Singletary, K., 2008. Cinnamon: overview of health benefits. Nutrition Today 43, 263-266.

Smith, J., Luo, Y., 2004. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol 64, 465-472.

Silverberg, G.D., Messier, A.A., Miller, M. C, Macha, J.T., Majmudar, S.S., Stopa, E.G., Donahue, J.E., Johanson, C.E., 2010. Amyloid efflux transporter expression at the blood-brain barrier declines. J. Neuropathol. Exp. Neurol 69, 1034-1043.

Strachan, M.W., Deary, I.J., Ewing, F.M., Frier, B.M., 1997. Is type II diabetes associated with an increased risk of cognitive dysfunction?: a critical review of published studies. Diabetes Care 20, 438-445.

Stavinoha, R.C. & Vattem, D.A., 2015. Potential neuroprotective effects of cinnamon. International Journal of Applied Research in Natural Products, 8, 24-46.

Tabatabaei-Malazy, O., Larijani, B., Abdollahi, M., 2015. Targeting metabolic disorders by natural products. Journal of Diabetes & Metabolic Disorders 14, 57.

Tahara, K., Kim, H.-D., Jin, J.-J., Maxwell, J.A., Li, L., Fukuchi, K.-i., 2006. Role of toll-like receptor signalling in Aβ uptake and clearance. Brain 129, 3006-3019.

Tong, H., Song, X., Sun, X., Sun, G. & Du, F., 2011. Immunomodulatory and antitumor activities of grape seed proanthocyanidins. Journal of agricultural and food chemistry, 59, 11543-11547.

Trevisan, M.T.S., Macedo, F.V.V., Van de Meent, M., Rhee, I.K., Verpoorte, R., 2003. Seleção de plantas com atividade anticolinasterase para tratamento da doença de Alzheimer. Quím Nova 26, 301-304.

Unlu, M., Ergene, E., Unlu, G.V., Zeytinoglu, H.S., Vural, N., 2010. Composition, antimicrobial activity and in vitro cytotoxicity of essential oil from Cinnamomum zeylanicum Blume (Lauraceae). Food Chem Toxicol 48, 3274-3280.

Vepsäläinen, S., Koivisto, H., Pekkarinen, E., Mäkinen, P., Dobson, G., McDougall, G.J., Stewart, D., Haapasalo, A., Karjalainen, R.O., Tanila, H., Hiltunen, M., 2013. Anthocyanin-enriched bilberry and blackcurrant extracts modulate amyloid precursor protein processing and alleviate behavioral abnormalities in the APP/PS1 mouse model of Alzheimer's disease. J Nutr Biochem 24, 360-370.

Wang, F., Pu, C., Zhou, P., Wang, P., Liang, D., Wang, Q., Hu, Y., Li, B., Hao, X., 2015. Cinnamaldehyde prevents endothelial dysfunction induced by high glucose by activating Nrf2. Cell Physiol Biochem 36, 315-324.

Wang, H., Zhang, C., Lu, D., Shu, X., Zhu, L., Qi, R., So, K.-F., Lu, D., Xu, Y., 2013. Oligomeric proanthocyanidin protects retinal ganglion cells against oxidative stress-induced apoptosis. Neural Regen Res 8, 2317.

Wang, J., Ferruzzi, M.G., Ho, L., Blount, J., Janle, E.M., Gong, B., Pan, Y., Gowda, Daniel Raftery, G.A.N., Arrieta-Cruz, I., Sharma, V., Cooper, B.S., Lobo, J., Simon, J.E., Zhang, C., Cheng, A., Qian, X., Ono, K., Teplow, D.B., Pavlides, C., Dixon, R.A., Pasinetti, G.M., 2012. Brain-Targeted Proanthocyanidin Metabolites for Alzheimer's Disease Treatment. J. Neurosci 32, 5144 -5150.

Wang, S.-Y., Chen, P.-F., Chang, S.-T., 2005. Antifungal activities of essential oils and their constituents from indigenous cinnamon (Cinnamomum osmophloeum) leaves against wood decay fungi. Bioresour Technol 96, 813-818.

Wang, J., Ho, L., Zhao, W., Ono, K., Rosensweig, C., Chen, L., Humala, N., Teplow, D.B. & Pasinetti, G.M., 2008. Grape-derived polyphenolics prevent Aβ oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. Journal of Neuroscience, 28, 6388-6392.

Wattanathorn, J., Chonpathompikunlert, P., Muchimapura, S., Priprem, A., Tankamnerdthai, O., 2008. Piperine, the potential functional food for mood and cognitive disorders. Food Chem Toxicol 46, 3106-3110.

Weinreb, O., Mandel, S., Amit, T., Youdim, M.B., 2004. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. J Nutr Biochem 15, 506-516.

Wenk, G.L., 2014. Your brain on food: How chemicals control your thoughts and feelings. Oxford University Press, USA.

Williams, R.J., Spencer, J.P., 2012. Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. Free Radic Biol Med 52, 35-45.

Williamson, G. & Manach, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. The American journal of clinical nutrition, 81, 243S-255S.

Wu, Y., Wu, Z., Butko, P., Christen, Y., Lambert, M.P., Klein, W.L., Link, C.D., Luo, Y., 2006. Amyloid-β-induced pathological behaviors are suppressed by Ginkgo biloba extract EGb 761 and ginkgolides in transgenic Caenorhabditis elegans. J Neurosci. 26, 13102-13113.

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

Xue, Y.-L., Shi, H.-X., Murad, F., Bian, K., 2011. Vasodilatory effects of cinnamaldehyde and its mechanism of action in the rat aorta. Vasc Health Risk Manag 7, 273.

Yanaga, A., Goto, H., Nakagawa, T., Hikiami, H., Shibahara, N., Shimada, Y., 2006. Cinnamaldehyde induces endothelium-dependent and-independent vasorelaxant action on isolated rat aorta. Biol Pharm Bull 29, 2415-2418.

Yao, Y., Huang, H.-Y., Yang, Y.-X. & Guo, J.-Y., 2015. Cinnamic aldehyde treatment alleviates chronic unexpected stress-induced depressive-like behaviors via targeting cyclooxygenase-2 in mid-aged rats. Journal of ethnopharmacology, 162, 97-103.

Youn, H.S., Lee, J.K., Choi, Y.J., Saitoh, S.I., Miyake, K., Hwang, D.H., Lee, J.Y., 2008. Cinnamaldehyde suppresses toll-like receptor 4 activation mediated through the inhibition of receptor oligomerization. Biochem Pharmacol 75, 494-502.

Youdim, K.A., Shukitt-Hale, B. & Joseph, J.A., 2004. Flavonoids and the brain: interactions at the blood–brain barrier and their physiological effects on the central nervous system. Free Radical Biology and Medicine, 37, 1683-1693.

Zamora-Ros, R., Knaze, V., Rothwell, J.A., Hémon, B., Moskal, A., Overvad, K., Tjønneland, A., Kyrø, C., Fagherazzi, G., Boutron-Ruault, M.-C., 2016. Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nutr 55, 1359-1375.

Zhang, B., Maiti, A., Shively, S., Lakhani, F., McDonald-Jones, G., Bruce, J., Lee, E.B., Xie, S.X., Joyce, S., Li, C., 2005. Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model. Proceedings of the National Academy of Sciences of the United States of America 102, 227-231.

Zhang, L., Zhang, Z., Fu, Y., Yang, P., Qin, Z., Chen, Y., Xu, Y., 2016a. Trans-cinnamaldehyde improves memory impairment by blocking microglial activation through the destabilization of iNOS mRNA in mice challenged with lipopolysaccharide. Neuropharmacol 110, 503-518.

Zhang, L., Zhang, Z., Fu, Y., Yang, P., Qin, Z., Chen, Y. & Xu, Y., 2016b. Trans-cinnamaldehyde improves memory impairment by blocking microglial activation through the destabilization of iNOS mRNA in mice challenged with lipopolysaccharide. Neuropharmacology, 110, 503-518.

Zhang, J., Mori, A., Chen, Q. & Zhao, B., 2006. Fermented papaya preparation attenuates β-amyloid precursor protein: β-amyloid–mediated copper neurotoxicity in β-amyloid precursor protein and β-amyloid precursor protein Swedish mutation overexpressing SH-SY5Y cells. Neuroscience, 143, 63-72.

Zhang, L., Wang, Y., Li, D., Ho, C.-T., Li, J. & Wan, X., 2016a. The absorption, distribution, metabolism and excretion of procyanidins. Food & function, 7, 1273-1281.

Zhao, H., Xie, Y., Yang, Q., Cao, Y., Tu, H., Cao, W., Wang, S., 2014. Pharmacokinetic study of cinnamaldehyde in rats by GC-MS after oral and intravenous administration. J Pharm Biomed Anal 89, 150-157.

Zhao, Q., Tang, X.C., 2002. Effects of huperzine A on acetylcholinesterase isoforms in vitro: comparison with tacrine, donepezil, rivastigmine and physostigmine. Eur J Pharmacol 455, 101-107.

Zhou, H., S Beevers, C., Huang, S., 2011. The targets of curcumin. Curr Drug Targets 12, 332-347.

Zhu, R., Liu, H., Liu, C., Wang, L., Ma, R., Chen, B., Li, L., Niu, J., Fu, M. & Zhang, D., 2017. Cinnamaldehyde in diabetes: A review of pharmacology, pharmacokinetics and safety. Pharmacological Research.

Zlokovic, B.V., 2004. Clearing amyloid through the blood-brain barrier. J Neurochem 89, 807-11.

Table 1. Plant species capable to improve AD

Table 2. Cinnamon bioactive compounds and their main physiological actions

Table 3. Bioactive components of cinnamon *spp.* with neuroprotective effects (those that mediate or initiate AD induction via different pathways or routes are included)

Fig. 1. Therapeutic efficacy of cinnamon *spp.*

Fig. 2. Schematic representation of cinnamon to prevent/ abrogate AD by reducing the Aβ and tau aggregation, inhibition of AChE activity, and also by inhibiting the oxidative stress elements and initiation of pro-inflammatory parameters

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Cinnamon, a promising prospect towards Alzheimer's disease.

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Author information

Abstract

Over the last decades, an exponential increase of efforts concerning the treatment of **Alzheimer's disease** (AD) has been practiced. Phytochemicals preparations have a millenary background to combat various pathological conditions. Various **cinnamon** species and their biologically active ingredients have renewed the interest **towards** the treatment of patients with mild-to-moderate AD through the inhibition of tau protein aggregation and prevention of the formation and accumulation of amyloid-β peptides into the neurotoxic oligomeric inclusions, both of which are considered to be the AD trademarks. In this review, we presented comprehensive data on the interactions of a number of **cinnamon** polyphenols (PPs) with oxidative stress and pro-inflammatory signaling pathways in the brain. In addition, we discussed the potential association between AD and diabetes mellitus (DM), vis-à-vis the effluence of **cinnamon** PPs. Further, an upcoming **prospect** of AD epigenetic pathophysiological conditions and **cinnamon** has been sighted. Data was retrieved from the scientific databases such as PubMed database of the National Library of Medicine, Scopus and Google Scholar without any time limitation. The extract of **cinnamon** efficiently inhibits tau accumulations, Aβ aggregation and toxicity in vivo and in vitro models. Indeed, **cinnamon** possesses neuroprotective effects interfering multiple oxidative stress and pro-inflammatory pathways. Besides, **cinnamon** modulates endothelial functions and attenuates the vascular cell adhesion molecules. **Cinnamon** PPs may induce AD epigenetic modifications. **Cinnamon** and in particular, cinnamaldehyde seem to be effective and safe approaches for treatment and prevention of AD onset and/or progression. However, further molecular and translational research studies as well as prolonged clinical trials are required to establish the therapeutic safety and efficacy in different **cinnamon** spp.

KEYWORDS: Alzheimer **disease**; Cellular pathway; **Cinnamon**; Neurocognitive performance

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