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Review

Cinnamon, a promising prospect towards Alzheimer's disease

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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.

Abbreviations: AD, Alzheimer's disease; PPs, polyphenols; EGCG, epigallocatechin gallate; NFTs, neurofibrillary tangles; ACh, acetylcholine; Aβ, amyloid-beta; APP, amyloid precursor protein; PS-1, presenilin-1; PS-2, presenilin-2; AChE, acetylcholine esterase; Cdk5, cyclin-dependent kinase 5; GSK3, glycogen synthase kinase 3; NaB, sodium benzoate; BBB, blood brain barrier; HEK293, human embryonic kidney; PNC, (2R,3S)-pinobanksin-3-cinnamate; MDA, malondialdehyde; SOD, superoxide dismutase; ROS, reactive oxygen species; sAPPβ, secreted amyloid precursor protein β; CHO, Chinese hamster ovary; 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; P-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-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; NO, nitric oxide; LPS, lipopolysaccharide; TLR4, ligand-induced toll-like receptor 4; TDI, tolerable daily intake; LD50, 50% lethal dose; PKA, protein kinase A; PHFs, paired helical filaments; cAMP, cyclic AMP; GST, glutathione S-transferase; NQO1, NAD(P)H-quinone oxidoreductase; TNF, tumor necrosis factor; BDNF, brain derived neurotrophic factor; NT-3, neurotrophin-3; CNS, central nervous system; CSF, cerebrospinal fluid; RAGE, receptors for advanced glycation end-products; LRP-1, lipoprotein receptor-related protein 1; P-gp, P-glycoprotein; cGMP, cyclic guanosine monophosphate; DM, diabetes mellitus; 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 deacetylase; USFDA, United States Food and Drug Administration; GRAS, generally recognized as safe; DPPH, 2,2-diphenyl-1-picrylhydrazyl; TA, thioacetamide; HDPC, human dental pulp cells.

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Contents

1. Introduction

According to statistics, there were 46.8 million people worldwide encountering dementia in 2015 and this number will ascend to 131.5 million in 2050 [205]. 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, DM and cognitive impairments [73]. 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 [65]. 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 AD [53,207].

Basically, amyloid plaques have been structured of amyloid-beta (Aβ) containing 39–42 amino-acid peptides that results from the sequential cleavage of the 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 [65]. 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 [103,169]. In this process, 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 deposition of Aβ [66,132].

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, so 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 that have been implicated in tau hyperphosphorylation such as cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3 (GSK3). Both Aβ and tau induce toxicity in AD via the procedures that are fully regulated by different kinases and phosphatases [26].

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 [76]. Regularly, these tangles are formed in the late stages of AD in association with amyloid formation [151]. The amount of NFTs has also been linked to the severity of dementia in AD [11]. It has been proposed that hyperphosphorylated tau may contribute in neuronal dysfunction even before its deposition [178]. On the other hand, tau is known to regulate neuronal excitability and hyperphosphorylated tau suppresses pre-synaptic protein expression and causes dysfunctional regulation of neuronal signaling and synaptic function that contribute to AD [131,23]. Plethora studies have pointed out that phosphorylated tau is essential for Aβ-induced neurotoxicity and cognitive decline [6,168]. In 2011, Ittner and Götz proposed that 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

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Table 1
Plant species capable to improve AD.

Plant species	Family	Part of plant	Type of inhibition	concentration	Model/Assay	References
Ginkgo biloba	Ginkgoaceae	Leaves	AChE	15 & 30 mg/kg/day	*In vivo*/scopolamine induced mice	Das et al. [38]
Paullinia cupana	Spindaceace	Seeds	AChE	1.5 mg/ml	*In vitro*/Ellmann's microplate assay	Trevisan et al. [191]
Amburana earensis	Fabaceae	Stem bark	AChE	2.3 mg/ml	*In vitro*/Ellmann's microplate assay	Trevisan et al. [191]
Lippia sidoides	Verbenaceae	Leaves	AChE	2.2-2.8 mg/ml	*In vitro*/Ellmann's microplate assay	Trevisan et al. [191]
Galanthus caucasicus	Amaryllidaceae	Bulbs, leaves, stems, flowers and roots	AChE	24 mg/day	*In vivo*/randomized clinical trial	Singh et al. [182]
Lycopodium cernua	Lycopodiaceae	–	AChE	IC_{50} = 42.6 μg/ml	*In vitro*/enzymatic assay on human blood	Konrath et al. [100]
Buxus hyrcana	Buxaceae	Leaves	AChE	IC_{50} = 443.6 ± 15.1 μM	*In vitro*/Ellmann's microplate assay	Choudhary et al. [32]
Aconitum falconer	Ranunculaceae	Root	AChE	IC_{50} = 278 ± 3.6 μM	*In vitro*/Ellmann's microplate assay	Atta-ur-Rahman et al. [12]
Iryanthera megistophylla	Myristicaceae	Stem bark	AChE	0.8 mg/ml	*In vitro*	Ming et al. [127]
Corydalis ternata	Papaveraceae	Tuber	AChE	IC_{50} = 0 50 μM	*In vitro*/Ellmann's microplate assay In vivo/mice	Kim et al. [96]
Sarcococca saligna	Buxaceae	Leaves	AChE	IC_{50} = 2.86 ± 0.07 mg/ml	*In vitro*/Ellmann's microplate assay	Kalauni et al. [88]
Catharanthus roseus	Apocynaceae	Root	AChE	IC_{50} = 0.775 μM	*In vitro*/Ellmann's microplate assay	Pereira et al. [152]
Piper nigram	Piperaceae	Seeds	AChE	IC_{50} = 65.16± 78.13 μM	*In vitro*/Ellmann's microplate assay	Ingkaninan et al. [74]
Zingiber officinale	Zingiberaceae	Rhizomes	AChE	IC_{50} = 2.86 ± 0.07 mg/ml	*In vitro*/Ellmann's microplate assay	Oboh et al. [133]
Cinnamonum tamala	Lauraceae	Bark	AChE	IC_{50} = 108.43 ± 0.331 μg/ml	*In vitro*/Ellmann's microplate assay	Dalai et al. [36]
Poncirus trifoliata	Rutaceae	Fruits	AChE	1200 mg/kg/bw	*In vivo*/mice	Kim et al. [95]
Salvia officinalis	Lamiaceae	Leaves	AChE	60 drops *d* ay	*In vivo*/randomized and placebo-controlled trial	Akhondzadeh et al. [5]
Scrophularia buergeriana	Scrophulariaceae	Root	AChE	2 mg/kg/bw	*In vivo*/mice	Jeong et al. [85]
Huperzia serrata	Lycopodiaceae	–	AChE	10 μM	*In vitro*/Ellmann's microplate assay	Zhao and Tang [219]
Bacopa Monnieri	Scrophulariaceae	Aerial parts	AChE	0.1 mg/ml	*In vivo*/mice	Das et al. [38]
Galanthus woronowii	Amaryllidaceae	Bulbs	AChE	0.18 μM	*In vivo*/mice	Mukherjee et al. [132]
Magnolia officinalis	Magnoliaceae	Bark	AChE	10 mg/kg	*In vivo*/mice	Lee et al. [108]
Coriandrum sativum	Apiaceae	Leaves	AChE	15% w/w of diet	*In vivo*/mice	Mani et al. [122]
Achyrocline tomentosa	Asteraceae	Leaves	AChE	IC_{50} = 0.4847 mg/ml	*In vitro*/Ellmann's microplate assay	Carpinella et al. [22]; Kim et al. [95]
Eupatorium viscidum	Asteraceae	Leaves	AChE	IC_{50} = 0.4792 mg/ml	*In vitro*/Ellmann's microplate assay	Carpinella et al. [22]
Ruprechtia apetala	Polygonaceae	Leaves	AChE	IC_{50} = 0.0779 mg/ml	*In vitro*/Ellmann's microplate assay	Carpinella et al. [22]
Trichocline reptans	Asteraceae	Leaves	AChE	IC_{50} = 0.1118 mg/ml	*In vitro*/Ellmann's microplate assay	Carpinella et al. [22]
Zanthoxylumcoco	Rutaceae	Leaves	AChE	50 mg/ml	*In vitro*/Ellmann's microplate assay	Carpinella et al. [22]
Poncirus trifoliate	Rutaceae	Leaves	AChE	400 mg/kg	*In vivo*/mice	Kim et al. [95]
Teucrium polium	Lamiaceae	Aerial parts	Aβ	1 mg/ml	*In vivo* mice/spectrophotometric Ellman method	Orhan and Aslan [138]
Punica granatum	Lythraceae	Husk	Aβ	IC_{50} = 14.83 ± 0.73 mg/l	*In vitro*	Bekir et al. [17]
Vitis vinifera	Vitaceae	Seeds	Aβ	IC_{50} = 1.04 ± 0.05 μM	*In vitro*	Jang et al. [261]
Carica papaya	Caricaceae	Fruits	Aβ	2.4 mg/ml	*In vitro*/SH-SY5Y cells	Zhang et al. [217]
Camellia sinesis	Theaceae	Leaves	Aβ	IC_{50} = 0.03 ± 0.004 mg/ml	*In vitro*	Okello et al. [136]
Juglans regia	Juglandaceae	Fruits	Aβ	10 μM	*In vitro*	Chauhan et al. (2004)
Crocus sativus	Iridaceae	Stigmas	Aβ	100 μg/ml	*In vitro*	Papandreou et al. [142]
Ginkgo biloba	Ginkgoaceae	Leaves	Aβ	100 μg/ml	*In vivo*/transgenic *Caenorhabditis elegans*	Wu et al. [206]
Withania Somnifera	Solanaceae	Root	Aβ	6.25–50 μg/ml	*In vitro*	Kumar et al. [102]
Paenoia suffruticosa	Paeoniaceae	Whole plant	Aβ	800 mg/kg/day	*In vivo* mice/Tg2576 APPswe mice	Fujiwara et al. [57]
Uncaria rhynchophylla	Rubiaceae	Whole plant	Aβ	10 μg/ml	*In vitro*/fluorescence spectroscopy	Fujiwara et al. [56]
Polygalae radix (root of P. tenuifolia)	Polygonaceae	Root	Aβ	10,20,40,100 μg/ml	*In vitro*/CHO cells	Lin et al. (2011)
Melissa officinalis	Lamiaceae	Leaves	Aβ	60 drops/day	*In vivo*/human clinical trials	Akhondzadeh et al. [4]
Curcuma longa	Zingiberaceae	Rhizomes	Aβ	10 &50 M	*In vitro*	Ono et al. [137]
Curcuma longa	Zingiberaceae	Rhizomes	Tau	10 μg/ml	*In vitro*/PC12 cells	Park et al. [145]
Myrica cerifera	Myricaceae	Root-bark	Tau	–	*In vitro*/M17 neuroblastoma cells	Jones et al. [87]
Camellia sinensis	Theaceae	Leaves	Tau	250 & 625 mg/kg/day	*In vivo*/primary hippocampal neurons	Li et al. [111]
Cinnamomum zeylanicum	Lauraceae	Bark	Tau	0.11 mg/ml	*In vitro*	Peterson et al. [151]
Vitis vinifera	Vitaceae	Seeds	Tau	150 mg/kg bw/day	*In vivo*/JNPL3 mice	Wang et al. [199]
Salvia officinalis	Lamiaceae	Leaves	Tau	36 μg/ml of rosmarinic acid	*In vitro*/PC12 cells	Iuvone et al. [77]
Salvia miltiorrhiza	Lamiaceae	Leaves	Tau	10 μM of Tanshinone IIA	*In vitro*/primary cortical neurons	Shi et al. [179]
Taxus yunnanensis	Taxaceae	Stem	Tau	10 μM of Taxus compounds A, C, E	*In vitro*	Ohtsuki et al. [134]
Panax ginseng	Araliaceae	Root	Tau	10 mg/kg/day of Ginsenoside Rd 2.5 & 5 μmol/l of Ginsenoside Rd	*In vivo*/rats *In vitro/primary cortical neurons*	Li et al. [110]
Allium sativum	Amaryllidaceae	Bulb	Tau	3 g/mouse	*In vivo*/Tg2576 mice	Chauhan [25,26]

AChE: acetylcholine esterase; Aβ: amyloid beta; –: not found.

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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 [125]. 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 globally well-known plant that applies as a generic term and 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) [28]. 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 the highest amount of cinnamon used around the world. Cinnamon bioactive compounds possess potent therapeutic efficiency in DM [18,21,107], cancer [98,192], oxidative stress [165], cardiovascular disease [71], wound healing [89], inflammatory syndromes, cholesterol levels and immunomodulatory diseases [82,156]. Additionally, cinnamon preparations were being used traditionally for centuries because of their neurostimulant, carminative, antibacterial and antifungal properties [24,58,165] (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 [8,55,151].

Cinnamon is reputed from both nutritional and pharmacological points of view and its beneficial health promoting properties is mainly attributed to the polyphenolic composition and the volatile essential oils coming from 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 and the camphor is the main compound in roots. Coumarins, phenolic acids, terpenes, tannins, mucus and carbohydrates were identified to be biologically active [135,183]. Catechin and epigallocatechin gallate (EGCG) were found to be the major phenolic compounds in cinnamon (mostly responsible for its antioxidant potential), whereas cinnamylaldehyde is the main compound of the volatile oils (Table 2). Regarding the nutritional values, ground cinnamon approximately encompasses 11% water, 81% carbohydrates (including 53% dietary fibre), 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) [193].

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 [15]. Medicinal amounts of cinnamon were reported safe, but it may become questionable when is used in excessive doses or over a long term [47]. No adverse reports have been cited in all the human studies involving cinnamon or its aqueous extracts [9]. An acute oral toxicity assay showed that cinnamon extract was safe at doses below 0.5 g/kg/bw, once was fed to Wistar rats [3]. 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 [10]. Cinnamon bark oil may cause skin sensitization, which limits its utilization in cosmetic and topical products [64]. While cinnamon bark is famed to cause drug interactions with hypoglycemic medicines, potential interactions with blood thinners such as warfarin and aspirin is also labeled as significant and may raise bleeding and bruising in patients taking warfarin and cinnamon bark, hence it should be monitored closely [45,46].

Mass spectrometric analysis has indicated that *C. verum* is much more pure than *C. cassia*, thus the daily consumption of *C. cassia* at 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 [79,135]. Today, coumarin is considered as a non-genotoxic compound with carcinogenic effect, as it might show hepatotoxic effect in sensitive groups [1]. High coumarin content of *C. cassia* may raise some safety concerns over prolonged consumption, but short-term trials have not reported any undesired effects [196]. 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 [167]. The Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food 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 [167]. 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 [2]

Within 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 [93]. USFDA and the council of Europe have approved cinnamaldehyde as a safe natural ingredient (daily intake of 1.25 mg/kg/bw), but it was mentioned that its high and non-nutritional consumption may cause genotoxicity and hepatotoxicity proven by *in vivo* and *in vitro* assays [221]. It was demonstrated that 50% median lethal dose (LD_{50}) of cinnamaldehyde (from *C. zeylanicum*) was 1850 ± 37 mg/kg/bw in Wistar rats [14]. This would be comparable with 11.4 ± 0.2 g/kg/bw in adult human [163]. Cinnamaldehyde has been characterized as a strong dermal sensitizer and a mucous membrane irritant [15]. 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, therefore reduces Aβ toxicity [55]. 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) [55]. Similar results were achieved whilst aqueous cin-

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Table 2
Cinnamon bioactive compounds and their main physiological actions.

	Biological activity	Experimental model	Active concentration/s	References
Essential oils				
Cinnamate	Antioxidant	High cholesterol fed rats	0.1 g/100 g of diet	Lee et al. [230]
	Improves hepatic lipid metabolism	High cholesterol fed rats	0.1 g/100 g of diet	Lee et al. [230]
Cinnamaldehyde	Anticancer	A375 human melanoma xenografts in SCID mice Human melanoma and colon cancer cell lines	120 mg/kg/bw IC_{50} < 30 Mm	Cabello et al. [231]
	Antidiabetic	Streptozotocin-induced diabetic rats	20 mg/kg/day	El-Bassossy et al. [49]
	Antimicrobial	Broth macrodilution assay; growth inhibition of *Escherichia coli*	400 mg/l	Pei et al. [232]
	Antiinflammatory	LPS-stimulated mouse macrophage (RAW264.7), Carrageenan –induced mouse paw edema	50 μM	Liao et al. [233]
	Antioxidant	Rat kidney	73.5 mg/kg/bw	Gowder and Devaraj [240]
	Cardioprotective	Isoproterenol-induced acute myocardial ischemia in rats	37.5, 75, 150 mg/kg/bw	Song et al. [226]
	Anti-tyrosinase	Murine B16 melanoma cells	4.04 mg/ml	Chou et al. [234]
	Immunomodulatory	Primary human alveolar macrophages, neutrophils & natural killer cells	Active at different concentrations	Clapp et al. [33]
	Hypolipidemic	C57BLKS db/db mice	20 mg kg/day	Li et al. [112]
Cinnamyl acetate	Anti-inflammatory	LPS-stimulated mouse macrophage (RAW264.7)	Not reported	Tung et al. [236]
2-methoxy-cinnamaldehyde				
	Nematicidal Activity	Direct contact bioassay (*Bursaphekchus xylophilus*)	0.887 mg/ml	Kong et al. [235]
Cinnamic alchohol	Anti- inflammatory	LPS-stimulated mouse macrophage (RAW264.7)	50 μM	Liao et al. [233]
	Antiproliferative	Murine colon 26-L5 carcinoma Murine B16-BL6 melanoma cells	47.8 μM 44 μM	Banskota et al. [237]
	Antifungal	Various species	100 ppm	Wang et al. [198]
Coumarin	Antibicrobial	Various species	Active at different concentrations	Shi and Zhou [238]
	Antifungal	Various species	100 ppm	Wang et al. [198]
	Anticancer	Non-small cell lung carcinoma NSCLC cell lines	100 μg/ml	Lopez-Gonzalez et al. [239]
	Anti-inflammatory	Thioacetamide (TA)-induced Intestinal injury in rats	Active at different concentrations	Witaicenis et al. [241]
	Anticogulant	Human blood	Not mentioned	Akoudad et al. [242]
	Antioxidant	Rats (different assays)	Active at different concentrations	Witaicenis et al. [241]
Eugenol	Antioxidant	Thioacetamide (TA)-induced hepatic injury in rats	10.7 mg/kg/bw	Yogalakshmi et al. [243]
		Swiss albino mice	150 mg/kg	Tiku et al. [244]
	Anti- inflammatory	Thioacetamide (TA)-induced hepatic injury in rats	10.7 mg/kg/bw	Yogalakshmi et al. [243]
	Anti-genotoxicity	Swiss albino mice	125, 250, 500 mg/kg/bw	Abraham (2001)
	Antinociceptive	Rats	50, 75 and 100 mg/kg	Daniel et al. [245]
	Neuroprotective	PC-12 cells	1–100 μM	Irie and Keung [246]
	Improves diabetic neuropathy and vasculopathy	Streptozotocin-diabetic rats	200 mg/kg/bw	Nangle et al. [247]
	Antifungal	Various species	100 ppm	Wang et al. [198]
	Antimicrobial	Various species	Active at different concentrations	Sanla-Ead et al. [248]
Poly phenolic compounds				
Cinnamic acid	Anticancer	CHO cells	148 μg/ml	Taner et al. [249]
	Antimicrobial	Various species	Active at different concentrations	Nascimento et al. [250]

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Table 2 (*Continued*)

	Biological activity	Experimental model	Active concentration/s	References
	Antioxidant	Cyclophosphamide-induced oxidative stress in Swiss albino mice	15, 30, 60 mg/kg/bw	Patra et al. [251]
	Antidiabetic	Diabetic rats/isolated mouse islets	5–10 mg/kg/bw	Hafizur et al. [252]
		FL83B cells	12.5 μM	Huang and Shen [253]
	Anti-genotoxicity	Human peripheral blood lymphocytes	148 μg/ml	Taner et al. [249]
	Anti- inflammatory	LPS-stimulated mouse macrophage (RAW264.7)	50 μM	Liao et al. [233]
	Cardioprotective	Isoproterenol-induced acute myocardial ischemia in rats	37.5, 75, 150 mg/kg/bw	Song et al. [226]
Catechins	Antioxidant	Scavenging of DPPH & authentic peroxynitrite	6.7 & 55.7 μM	Iacopini et al. [254]
	Antiproliferative	Pancreatic cell lines: Panc1, Panc89 & BxPC3	80 μM	Kurbitz et al. [255]
	Anti-inflammatory	Human dental pulp cells (HDPC)	10 μg/ml	Nakanishi et al. [256]
	Neouroprotective	Rats	10 & 20 mg/kg/bw	Ahmed et al. [257]
Quercetin	Antioxidants	Scavenging of DPPH & authentic peroxynitrite	5.5 & 48.8 μM	Iacopini et al. [254]
	Anti-inflammatory	Human C-reactive protein transgenic mice	12.9 ± 1.3 μM	Kleemann et al. [258]
	Neuroprotective	Transgenic *Caenorhabditis elegan*	250 μM	Jagota and Rajadas [259]
	Anticancer	MCF-7 cells	10–175 μM	Chou et al. [260]
Proanthocyanidins	Antioxidant	Scavenging of DPPH	IC_{50} = 87.36 μg/ml	Song et al. [226]
	Antiproliferative	Platinum-resistant human ovarian, neuroblastoma & prostate cancer cell lines	IC_{50} = 79–479 μg/ml	Singh et al. [229]
	Neuroprotective	Tg2576 AD transgenic mice	200 mg/kg/bw	Wang et al. [197]
		Diabetic Rats	500 mg/kg/bw	Ding et al. [228]
	Anti diabetic	Low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats	500 mg/kg/bw	Ding et al. [227]
	Anti-tyrosinas	Mushroom tyrosinase activity	IC_{50} = 54.8 μg/ml	Song et al. [226]
	Immunomodulatory	Peritoneal macrophages	50, 100, 200 μg/ml	Tong et al. [190]
	Hypolipidemic	Rat hepatocytes	250 mg/kg/bw	Baselga-Escudero et al. [16]

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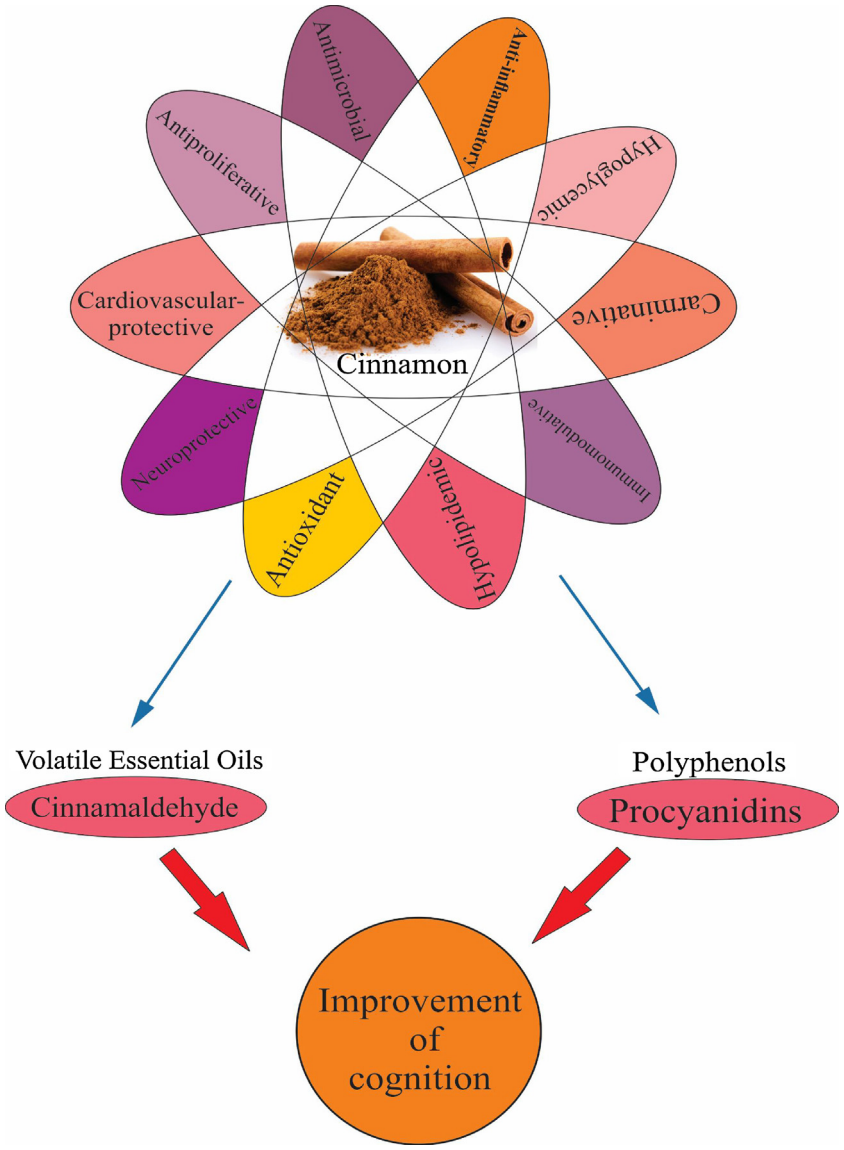

Fig. 1. Therapeutic efficacy of cinnamon spp. Figure was drawn according to the guidelines of the journal for preparing color figures [171].

namon 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 [55]. 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 [55].

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 tubulins 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 [151].

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 oxidative stress. Pre-incubation of tau 187 with cinnamaldehyde prior to initiation of aggregation was led to a greater retardation, in comparison to the time that cinnamaldehyde was introduced to the tau at the time of aggregation [59].

In vitro condition, human embryonic kidney (HEK293) cells transfected with GSK3 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 [44].

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 phos-

phorylated GSK3β (critical for choline metabolism), inhibited AChE activity and increased neuron number in hippocampus area of these animals [120]. 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) [36]. Besides, coumarins were also found to possess AChE inhibitory properties [7].

PPs such as EGCG 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) [109,180,92,141]. Cinnamyl alcohol (100 mg/ml) has also been reported to show inhibitory effects against AChE activity [144]. Furthermore, cinnamaldehyde prevented inflammation and suppressed the formation of NFs, thus the enhanced cinnamaldehyde levels might manipulate the cognitive function in the scopolamine-induced amnesia in mouse models [143]. 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 decreased the level of inducible nitric oxide synthase (iNOS) protein expression in rat injured brain tissues [30].

In a similar study, the neuroprotective effects of (2R, 3*S*)-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 [117].

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 [203]. 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 [115]. Proanthocyanidins are the recent subject of research [196] and are efficient scavengers of reactive oxygen species, therefore might be favorable for treatment of AD [149].

Cinnamic acid (45 and 90 mg/kg/bw for 21 days) was shown to improve depression, neuroinflammation and brain injury in rats [210]. 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 [213]. 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 secreted amyloid precursor protein β (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 [90]. 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 is ingested in 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 [121,204]. The ability of cinnamon to affect the nervous system will mostly depend on their metabolites ability to cross the BBB through the process of diffusion across the membrane and eventually enter the brain [176]. 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 [113]. 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. Despite this fact, there are certain animal studies which show the entry of glucuronides entry into the brain through BBB [50,212].

It was stated that people with poor learning ability have a low level of GABRA5 (gamma-aminobutyric acid type A receptor alpha5 subunit) and a high level of CREB (cAMP response element binding protein), 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 [128]. 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 [165]. 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 [128].

Flavonoids such as epicatechin and catechin, and their glucuronidated metabolites have been identified in the brain after acute and chronic administration along with grape seed polyphenolic extracts [50]. It has been confirmed that only the fractions of grape extract that contained polyphenols with monomeric structure like those of catechin and epicatechin can be accumulated in the brain approximately up to 400 nM as compared to the other oligomeric fractions of the extract [197]. 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 [197]. 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 aging and degenerative diseases such as AD [92].

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 Behl, 1997; [175]. 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 [51]. 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. On the other hand, oxidative stress may raise the production of Aβ oligomers by activating the enzyme that limits Aβ production, so facilitates amyloid plaque formation [39]. 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 effectually increased ferric reducing antioxidant power (FRAP) and plasma thiol (P-SH), lowered MDA levels, and elevated antioxidant enzyme activities of SOD and catalase (CAT) [129]; [172]. 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 was elevated, while the transaminase and lipid peroxidation (LPO) were reduced [52,164,166]. 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 realized 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 [35]. *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 glutathione oxidative stress parameter [78].

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; GST (glutathione S-transferase) and NQO1 (NAD(P)H-quinone oxidoreductase), that leads to the cell protection and enhances cell survival [123,160,161]. For instance, Kim and collaborators showed that 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 [94].

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 [83]. In a study, procyanidin type-A polymers (10 and 20 μg/ml) isolated from an aqueous extract of cinnamon lessened H_2O_2-induced downregulation of the atrophic factor, S100β secretion, through enhanced expression of SIRT1 in C6 rat glioma cells. This might be contributed to the suppression of the expressions of tumor necrosis factor alpha (TNF-α), NF-κB p65, and Bcl-2 family members [158]. It has been verified that S100B is associated with the principle mechanisms of neurodegeneration in AD [153]. 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 [159].

5.2. Cinnamon and pro-inflammatory function

Researchers illustrated that AD comprises strong interactions with chronic neuroinflammation [67]. Pro-inflammatory mediators (chemokines (IL-8, MIP-1a, MCP1, RANTES, eotaxin), interferons (IFN), interleukins (IL-1, IL-2, IL-6), lymphokines and TNFs), 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 the disease [104].

PPs are well characterized by their pro/anti-inflammatory functions [30,99]. 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 [70,91,161]. 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 [147]. 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 [60].

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-2 (COX-2)] are repressed [91]; [174]. 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 [72]. 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 [68].

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 effect occurred via the induction of Nrf2-(nuclear factor (Erythroid-Derived 2)-Like 2) related pathway mainly involved in the regulation of the intracellular thiol redox state [114]. Trans-cinammaldehyde has also been found to inhibit neuroinflammation via 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 [155,30]. Zhang and his group achieved the same results and offered this compound mediated MEK1/2-ERK1/2 signaling pathway in LPS-stimulated microglias in mice [216].

In addition, cinammaldehyde downregulated the ligand-induced toll-like receptor 4 (TLR4) oligomerization, NF-κB

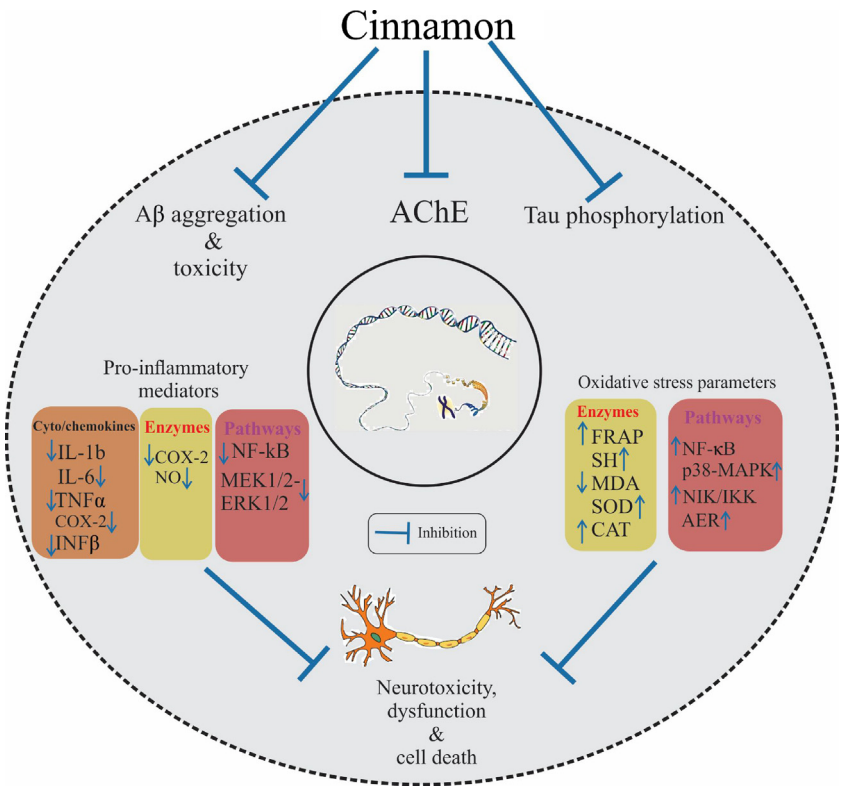

Fig. 2. Schematic representation of cinnamon to prevent/abrogate AD by reducing the Aβ and tau aggregation, inhibition of AChE activity, and also by inhibiting the oxidative stress elements and initiation of pro-inflammatory parameters.

activation and other target genes such as COX-2 and IFNβ in macrophages (RAW264.7) [211]. TLR4 has been reported as a mediator of AD and plays a critical role in the normal Aβ clearance [48,124,189]. 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 other immunochemicals (CD68, CD11c and CD11b). Inhibition of DNA-binding of NF-κB was introduced as the most likely anti-inflammatory mechanism of NaB [20]. It was suggested that NaB may pass through the BBB, so it could change the neuroimmunology of encephalomyelitis and ameliorate multiple sclerosis severity [139]. Fig. 2 depicts the effect of cinnamon on pathways involved in modulation and progression of AD.

Jana et al. [79] suggested that 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 (brain derived neurotrophic factor) and NT-3 (neurotrophin-3)) within the brain cells and CSN in mice through the activation of protein kinase A (PKA) and CREB. Further, oral feeding of NaB (250 μM) alone, activated the same mechanism and pathway in the central nervous system (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 that NFs protect neuronal cells from deprivation processes. Moreover, some NFs are reported to be remarkably suppressed in the brain of AD patients [148]. Jeon et al. demonstrated that a mixture of various neuroprotective compounds, including cinnamic acid, at low concentrations, synergistically exhibited stimulation of BDNF in neurological disease such as AD. This mixture also induced mRNA and protein expression through phosphorylation of ERK and CREB protein and inhibition of iNOS upregulation in cultured rat primary cortical neurons [84]. Likewise, cinnamic acid enhanced the BDNF release in cultured rat primary cortical neurons. It is known that eugenol has favorable effects for management of AD, as it can alleviate Aβ-induced neurotoxicity and increase the expression of BDNF gene in the hippocampus [75]. 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

Vascular defects, neural and vascular inflammation and brain endothelial dysfunction are frequently diagnosed in AD. Aβ peptides are scavenged from the brain through different mechanisms such as passage to the cerebrospinal fluid (CSF) with subsequent re-absorption into the venous circulation, and direct conduction across the BBB [222]. Aβ peptides are transported by receptors for advanced glycation endproducts (RAGE) to the perivascular space. It was shown 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 role for increased Aβ deposition and decreased clearance, respectively [185]. It has also been verified that the BBB endothelium has a potential role in production of Aβ through proteolytic processing of Aβ precursor protein [42]. 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 [173]. In addition, brain endothelial cells regulate the neuronal environment and any disruption in their function could result in formation of a

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

Compounds	Origin	Significant effects	Experimental model	References
Procyanidin A trimer 1	*C. burmannii*	Reduction of glial swelling by regulation of the intracellular Ca^{2+} movement	*In vitro* (glial cells)	Panickar et al. [140]
		Reduction of oxygen-glucose deprivation-induced neuronal damage	*In vitro* (organotypic hippocampal slices)	Qin et al. [158]
Procyanidin type-A polymers (CP)	*C. burmannii*	Regulation of S100β secretion by regulating SIRT1, suppression of TNF-α, NF-κB p65, Bcl-2	*In vitro* (glioma cells)	Jiao et al. [86]
Procyanidin type-A	–	Inhibition of misfolding of human islet amyloid polypeptide, DM inhibition	*In vitro* (INS-1 cells)	Lu et al. (2011)
	C. cassia	Increasing insulin sensitivity	*In vivo* (streptozotocin –induced diabetic mice) In vitro (HepG-2 cells)	Lu et al. (2011)
Procyanidin B2	*C. zeylanicum*	Inhibition of advanced glycation endproducts production	*In vitro* (bovine serum albumin-glucose model)	Peng et al. [149] and Peng et al. [150]
	C. cassia	Increasing insulin sensitivity	*In vivo* (streptozotocin –induced diabetic mice) *In vitro (HepG-2 cells)*	Lu et al. (2011)
Polyphenols mixture (cassiatannin A, cinnamtannin D1, cinnamtannin B1, 2 type A trimer isomers, type A polymers)	*C. burmannii*	Upregulation of SIRT, activation of MAPK, suppression of pro-inflammatory cytokines	*In vitro* (glioma cells)	Qin et al. [159]
Cinnamaldehyde	*C. cassia*	Reducing the expression of NO, IL-1b, IL-6, TNFα, NF-kB	*In vitro* (LPS induced BV2 microglia cells)	Ho et al. [68]
	C. cassia	Inhibiting TNFα-induced expression of cell adhesion molecules, suppresses NF-κB via IκB and Nrf2, reduces intracellular thiol redox	*In vitro* (endothelial cells)	Liao et al. [114]
	–	Suppression of iNOS mRNA, reduction in NO production, interruption of MEK1/2-ERK1/2 pathway	*In vitro* (LPS induced BV2 microglia cells)	Zhang et al. [215,216]
	–	Suppression of TLR4 oligomerization, NF-κB, COX-2, IFNβ	*In vitro* (macrophages)	Youn et al. [211]
	C. cassia	Vasorelaxant	*In vitro* (rat endothelial cells)	Xue et al. [208]
Trans-cinammaldehyde	*C. ramulus*	Inhibition of iNOS and COX-2	*In vivo* *In vitro (LPS induced BV2 microglia cells)*	Pyo et al. [155]
	–	Reduction of brain injury by inhibition of neuroinflammation	*In vivo*	Chen et al. [30]
		Reduction of expression of iNOS, COX-2, TNFα, P53, NF-kB	*In vitro* (LPS induced BV2 microglia cells	Chen et al. [30]
Cinnamophilin	*C. philippinense*	Protection against ischemic damage in brain cells, enhancement of neurobehavioral conditions	*In vivo*	Lee et al. [224]
	C. burmannii	Reduction of oxygen-glucose deprivation-induced neuronal damage in organotypic hippocampal slices	*In vivo*	Panickar et al. [140]
Catechin	*C. zeylanicum*	Inhibition of advanced glycation endproducts production	*In vitro* (bovine serum albumin (BSA)-glucose model)	Peng et al. [149] and Peng et al. [150]
Epicatechin	*C. zeylanicum*	Inhibition of advanced glycation endproducts production	*In vitro* (bovine serum albumin (BSA)-glucose model)	Peng et al. [149] and Peng et al. [150]
Phenylpropanoids (medioresinol & cryptamygin A)	*C. cassia*	Inhibition of β-secretase, Inhibition of Aβ40 production	*In vitro* (Chinese hamster ovary- APP_CHO cells)	Kang et al. [90]
NaB (cinnamon metabolite)	*C. cassia & C. verum*	Increasing BDNF and neurotrophin-3, induction of PKA–CREB pathway	*In vivo* (mouse CNS)	Jana et al. [79]
		Increasing BDNF and neurotrophin-3	*In vitro* (primary human neurons and astrocytes)	Khasnavis and Pahan [93]
	Not reported	Upregulates PD protein DJ-1, mediates mevalonate metabolites	*In vitro* (primary human neurons and astrocytes)	

toxic neuronal condition in AD patients' brain. Consequently, Aβ deposition happens and in turn Aβ stimulates the release of inflammatory mediators [62]. Toxic Aβ may also affect endothelial cells and cause endothelial-dependent vasoconstriction [146]. 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 NO, likewise motivated vascular smooth-muscle relaxation in patients with DM [13].

Yanga et al. claimed that cinnamaldehyde acts as a vasorelaxant on isolated rat aortas in an endothelium-dependent manner [209], 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 with both Ca^{2+} influx and Ca^{2+} release [208]. Cinnamaldehyde prevented the progress of hypertension in both types of DM by regulation of vascular contractility and affecting the production and activity of insulin in deficiency situations [49]. In addition, cinnamaldehyde attenuated vascular cell adhesion molecule-1 (VCAM-1) and sICAM-1 via inhibiting TNFα-induced expression of endothelial factors. It also suppressed their transcriptional levels by decreasing (sVCAM-1) and soluble intercellular

adhesion molecule-1 (sICAM-1) messenger RNA levels [114]. It is shown that cinnamaldehyde devoted a protective effect towards endothelial dysfunction under hyperglycemic conditions and this phenomenon was mediated by Nrf2 activation and up-regulation of downstream target proteins [195,198].

6.2. Cinnamon, AD, and DM

The probability that patients with type 2 DM ultimately experience AD is estimated to be soaring. That is why a number of references consider AD as a kind of DM. The term "type 3 DM/brain DM" has been raised to describe AD [101]. 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 [186]. In addition, insulin and insulin signaling mechanisms are imperative for neuronal survival, since the expression of the insulin receptors were lowered in AD patients [36,40]. A meta-analysis study published in 2010, reported that the obesity and DM significantly and independently increase the risk factors for developing AD [154]. In a comparative study of AD patients against non-AD group, 81% of AD patients showed either type 2 DM or impaired blood glucose levels [81]. Aforementioned, cinnamon persuades cellular antioxidant defense mechanisms. Moreover, it is well established that oxidative stress plays a major role in both DM and AD that are both affected by common elements [188]. Cinnamon PPs, catechin, epicatechin and procyanidin B2 showed significant inhibitory effects towards the formation of three typical advanced glycation end products (AGEs), which were ascribed to their antioxidant and carbonyl scavenging capacities [149,150].

Cinnamon and its components possess insulin-like or insulin-potentiating properties and can modulate glucose uptake and glucose uptake-related genes expression [34,157]. 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 administrated 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 Aβ accumulation and deposition, so improved cognitive dysfunction in hippocampal amyloid-β (25–35)-infused AD rats [143]. Cinnamon extract significantly inhibited the aggregation and formation of tau and amyloid precursor proteins, indicating that cinnamon could effectively improve insulin sensitivity [8]. In accordance, cinnamon proanthocyanidins were found to inhibit the misfolding of human islet amyloid polypeptide, a proposed causative factor for DM [86]. Lu and teammates also verified cinnamon procyanidin oligomers (type A and B) may improve insulin sensitivity [225].

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 [181]. 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?

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 [215] and has shown low bioavailability (<20%) and stability when was fed to rats (50 mg/kg/bw) [223]. Cinnamaldehyde has a half-life of 6.7 h and is stable in rat plasma at room temperature for 24 h post oral administration [218]. Although, it is assumed that cinnamaldehyde is well distributed throughout the body after absorption [221] and its low water solubility may confine its pharmacological effectiveness [63]. HPLC analysis exhibited that 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 [29]. 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 dependent on the quantity of its metabolites [221]. 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 compound (2′-hydroxycinnamaldehyde) was detected at a considerable level [105,106,221].

It was illuminated that procyanidins (monomers to polymers) might face some limitations regarding absorption or transition along the intestinal tract [130]. The decomposition of these compounds is dependent on the pH value of gastric juice and diet intake. Methylated and glucuronidated procyanidins dimers and monomers are their main metabolites found in the plasma [216]. Recently, the pharmacokinetic examination of cinnamon barks (1 g/kg/bw) following ingestion showed that various metabolites of epicatechin and procyanidins were detectable in the urine and feces of rats. Further, it was found that 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 higher than it was supposed earlier [126]. Besides, the polymeric structures of catechin and epicatechin were not frequently bioavailable as their monomeric forms [151]. Today, various formulation strategies such as nanoparticles, lipids carriers, self-emulsifying and solid dispersions are employed to overcome such defects.

Along with chemical structures, PPs molecular weight, their interactions with BBB and other substrate transporters of the brain blood circulation system, are considered as determinants factors [181]. It was evidenced that proanthocyanidins isolated from grapes could pass throughout the BBB [80]. Furthermore, it has been suggested that brain deposition of PPs is directly affected by the number of dosing rather than a single supplementation [181,54].

Taking collectively, the bioavailability and brain permeability of cinnamon components are not clarified yet and needs more investigation. 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 that long-term *in vivo* experimental designation seems necessary to assess Aβ pathology in AD patients, since prolonged supplementation of anthocyanin may inhibit Aβ- aggregation *in vivo* models but not *in vitro* cells [194]. 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. [61]. Based on their conclusion, the clinical trials on hyperglycemic properties of cinnamon are the 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 [162]. Yet,

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the fact that whether cinnamon is able to act as a neuroprotective agent *in vivo* condition remains controversial.

8. Cinnamon, AD and epigenetics, a promising prospect

Epigenetic means the stable and heritable changes in the chromatin structure that may influence gene expression [119]. Epigenetic modifications are typically classified as DNA methylation, histone post-translational changes and microRNAs (miRNAs). Irregular regulation of epigenetic mechanisms has been linked to AD and other neuronal dysfunctions [69]. A great body of evidence testifies that patients with AD have an aberrant DNA methylation profile in both early and late stages of the disease [19]. It has also been stated that the balance between histone acetylation and deacetylation is lost in AD [43].

Dietary PPs may be able to induce epigenetic alterations and eventually mediate the gene expression with profound importance regarding some disease, particularly AD. For instance, some dietary nutrients and a number of phytochemicals such as PPs showed to be effective concerning DNA methylation and histone acetylation [31]. Although no attempt has been made to study the epigenetic properties of cinnamon so far, nonetheless few compounds have been evaluated from the other plant resources. For example, EGCG isolated from green tea inhibited DNA methylation and contributed to histone post-translational modifications through the inhibition of histone deacetylase (HDAC) [19]. It has been defined that cinnamon PPs also inhibited HDAC [116]. SIRT1 a member of HDAC family is reported to be involved in AD pathology [41]. Quercetin, a polyphenolic compound, also found in cinnamon spp. has been shown to increase mRNA expression of SIRT1 in mice and activated SIRT1-induce deacetylation of histone H3 in human prostate cancer cells [37,97].

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. Of course, pharmacokinetic studies of the bioavailability and bioefficacy of cinnamon bioactive molecules raise some 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 accumulation, 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 the gene expression profiles. As the main bioactive components of cinnamon spp. cinnamaldehyde and procyanidins are found to suppress AD and interrupt both oxidative and inflammatory cascade of actions within 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. Totally, cinnamon strongly abrogates neurodegeneration procedure and displays remarkable neuroprotective effects in AD models via multiple routes.

Conflict of interest statement

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

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