Pharmacological Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

# Cinnamon, a promising prospect towards Alzheimer's disease

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ARTICLE INFO

*Article history:*
Received 13 September 2017
Received in revised form
10 December 2017
Accepted 10 December 2017
Available online xxx

*Keywords:*
Cinnamon
Alzheimer disease
Neurocognitive performance
Cellular pathway

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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https://doi.org/10.1016/j.phrs.2017.12.011
1043-6618/

**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

Please cite this article in press as: S. Momtaz, et al., Cinnamon, a promising prospect towards Alzheimer's disease, Pharmacol Res (2017), https://doi.org/10.1016/j.phrs.2017.12.011