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VIEWS AND REVIEW

Therapeutic potential of cinnamon for neurological disorders: A mini-review

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Abstract

An increasing amount of evidence suggests that cinnamon, due to its rich source of polyphenol content, may exert antioxidant and anti-inflammatory properties, hence could be used in the treatment of variety of diseases. in this regard, many studies explored the effects of cinnamon and its bioactive components (coumarin, cinnamic acid, cinnamaldehyde and type A procyanidin polymers) on various neurological diseases including Parkinson's disease, neuroinflammation, multiple sclerosis, brain injury, Alzheimer's disease, migraine, and hyperactivity. The present study attempts to review available data concerning the therapeutic potential of cinnamon and its derivatives in neurological disorders.

Keywords: Cinnamon, trans-cinnamaldehyde, cinnamaldehyde, neurological disorders, natural medicine

INTRODUCTION

The term "neurological disorder" refers to any condition that impairs the normal structure and function of the nervous system**.** Neurological disorders are ranked as the second leading cause of death worldwide and the first leading cause of disability since patients usually present with cognitive decline or sensorimotor dysfunction that may drastically reduce the quality of daily activities.[1] This high rate of mortality and morbidity indicates the importance of preventive and therapeutic approaches. due to complications of conventional drugs used for treating neurological conditions, the therapeutic potential of natural products has become the focus of many studies in recent years. Cinnamon is a spice widely known for its use in food seasoning, with remarkable properties that have benefited traditional medicine for alleviating symptoms of various diseases through centuries.[2,3] Over the past few decades, many studies investigated the logic behind remedial effects of cinnamon, and according to their results, cinnamon is rich in components with anti-inflammatory and antioxidant properties. Cinnamon contains trans-cinnamaldehyde (TCA), cinnamaldehyde as well as camphor, eugenol and other bioactive compounds[4] with TCA and cinnamaldehyde being the most effective ones.[5] The concentration of each component in different forms of cinnamon affects the possible post-prescription outcomes. Owing to its therapeutic properties, cinnamon could be useful in conditions associated with the increased mount of oxidants and pro-inflammatory biomarkers, including nervous system disorders. Several animal and cellular investigations and

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clinical trials have revealed the neuroprotective role of cinnamon and its extracts in the prevention and treatment of different neurological disorders. The eugenol has been found to be neuroprotective with possible application to treatment of Alzheimers disease, depression, and Parkinson disease.[6] It has been shown that cinnamon exerts not only neuroprotective activity through suppressing the inflammation and oxidative injury in traumatic brain injury but also might have a therapeutic role in traumatic brain injury-related dementia with its well-known cognitive enhancer and anti-amyloid effects.[7] TCA is known to safely reduce inflammation in microglia, neural damage, apoptosis[8,9], myelin degeneration[10], dysfunctional protein aggregation, and overall function of the nervous system.[11,12] Considering these findings, cinnamon with multipotential neuroprotective properties, relevant clinical therapeutic effects, and superior safety profile might be a noteworthy candidate for the treatment of neurological disorders. This paper aims to discuss the potential impact of cinnamon consumption on neurological disorders, based on relative studies and publications.

METHODS

This study aimed to gather and present information on the therapeutic potential of cinnamon on neurological disorders by covering original articles on this subject published up to December 2020. For this purpose, several databases such as Scopus, Google search, Google Scholar, Web of Science, and PubMed were thoroughly searched. These keywords included terms such as nervous system, neurological diseases, cinnamon, brain injury, neurobehavioral alterations, hyperactivity disorders, AD, neuroinflammation, encephalomyelitis, PD, brain insulin impairment, depression, anxiety, and brain-derived neurogenesis factor.

NEUROINFLAMMATION

Neuroinflammation is defined as the activation of the brain's innate immune system in response to inflammation and is characterized by a myriad of cellular and molecular alterations inside the brain. The fact that the extent of inflammation effects on tissues depends on the time of diagnosis and receiving interventions has attracted the interest of researchers to approach more efficient and effective treatments.[13] It is suggested that the management of neuroinflammation can decelerate the progress of neurodegenerative disorders. It has been proven that cinnamon has effects on ameliorating neuroinflammation and recent studies have provided more knowledge about cinnamon's anti-inflammatory role and so far, TCA has shown strong anti-inflammatory capability among the eight tested fractions of cinnamon. Natural cinnamaldehyde and Its derivatives were shown to ameliorate neuroinflammatory pathways in neurodegenerative diseases.[14] Several studies have assessed the effects of TCA on lipopolysaccharide (LPS) induced pro-inflammatory responses in BV2 microglial cells. TCA pretreatment considerably reduced LPS-induced production of pro-inflammatory mediators such as nitric oxide (NO), inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2), interleukin-1β (IL-1β), and Tumor necrosis factor-alpha (TNF-α) without affecting cell viability and improved the morphological changes in BV2 microglial cells. TCA also blocked the transcription of nuclear factor kappa B (NF-κB), a signaling pathway involved in the inflammation process, increased cytosolic inhibitor alpha (IκBα), and up-regulated tumor protein 53 (P53), an important contributor to cellular response against stress which inhibits NF signaling pathway resulting in an increased survival rate of BV2 microglial cells.[8,9,15] Moreover, Schink *et al*.[16] demonstrated that TCA and p-cymene exerted more efficient anti-inflammatory activity than other constituents of cinnamon extract (CE) via affecting toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) signaling pathways. In the absence of cinnamon compounds, TLR2 and TLR4 stimulation via LPS induced the production of inflammatory cytokines in HEK-TL R4 and HEK-TLR2 cells.[17] While TCA and p-cymene treatment considerably inhibited the LPS-dependent IL-8 secretion and NF-κB activation.[16] Also, In THP-1 monocytes, Cinnamon compounds impaired the phosphorylation of protein kinase B (Akt) and restored cytosolic IκBα, two important mediators inducing the transcriptional activity of NF-κB.[16,18] In vivo effects of cinnamon on neuroinflammation have also been examined. TCA (oil in the cinnamon powder) was administered 3 hours after the injection of LPS and continued for a week. The results showed that TCA considerably improved the impaired function of hippocampus in subject mice and decreased pro-apoptotic and pro-inflammatory mediators.[19] Also, in another study, treatment with TCA considerably reduced the infarcted area in mice with induced ischemic/reperfusion brain injury.[20]

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is one of the main causes of death in individuals under 45 years of age.[21] This condition occurs as a result of mechanical stress (primary damage) to the brain followed by edema, inflammatory processes, and chain injuries (delayed and secondary damage) that lead to neurological and behavioral disorders. Oxidative damage and neuroinflammation are two important factors promoting lesion formation in brain tissue, nerve cell damage and loss.[22] Cinnamon has been shown to play a role in the treatment of brain injury. Yulug *et al*.[23] measured the effect of cinnamon polyphenol extract on TBI in male mice subjected to cold trauma. treatment with CE resulted in neuron protection, inhibited injury-induced death of neurons by suppressing inflammation and oxidative damage, and also improved the histopathological outcomes of TBI.[23] In a similar study conducted by Qubty *et al*.[24] components of CE, after metabolism in the gut and liver, were able to cross the blood-brain barrier and enter the brain, which could explain why complications of brain damage (cognitive-behavioral problems) such as memory loss and post-concussion syndrome improved in the treatment group. Overall, these studies suggested that a diet pattern with cinnamon constituents can attenuate cognitive/behavioral dysfunction.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder, usually diagnosed during childhood, and is observed in about 5% of school-age children. Common symptoms include lack of attention, excessive activity, and impulsivity.[25,26] Despite the benefits of medication, rehabilitation, and behavioral therapy for the treatment of neurobehavioral diseases such as ADHD, the side effects of medications have raised concern. In this regard, Chen *et al*.[27] evaluated the potential of cinnamon when applied besides rehabilitation, for the treatment of ADHD in children. Twenty patients,16 boys and 4 girls with a mean age of 4 years, with ADHD were divided into control and experimental groups. The control group was only recruited for the rehabilitation program, while the experimental group received both cinnamon therapy and rehabilitation. children's parents were asked to answer the SNAP_IV questionnaire pre- and post-treatment to assess the child's activity score. The analysis of collected data showed more positive behavioral changes regarding the experimental group than the control group.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD), an irreversible neurodegenerative disorder with cognitive symptoms such as confusion, memory loss, impaired judgments, and reduction of language skills.[28] In elders, it is one of the main causes of senile dementia, characterized by neuronal degeneration and cognitive deterioration[29] The accumulation of soluble oligomeric assemblies of amyloid-beta (Aβ) polypeptides and neurofibrillary tangles plays a crucial role in the pathogenesis of AD, therefore natural sources with properties that are able to impair plaque or tangle formation have gained interest.[30] In a study exploring the anti-AD potential of CE, it was shown that inhibition of Tau fibrillation occurred after CE administration with no harm to physiological tau function, suggesting CE as a safe approach to AD treatment.[31] Interestingly, George *et al*.[32] tested the effects of cinnamaldehyde and epicatechin, a component derived from active cinnamon extract, on tau fibrillation. In this study, CE and the oxidized form of epicatechin were able to interfere with neurofibrillary tangle formation through binding with the thiol side-chain of cysteines, the amino acids present in tau structure. Favorably, this bound was found to be reversible, allowing tau to preserve its biological function and assemble to tubulin. Also, the anti-oxidative activity of these compounds protected tau from oxidative damage induced by ROS. Epicatechin in particular, acting as a scavenger, inhibited the reaction between tau proteins and highly reactive byproducts of oxidation process. these oxidation reactions, if not prevented early, could result in forming high molecular weight substances promoting tau aggregation. Moreover, there are few studies observing the protective activities of cinnamon's water-soluble extract against AD in mice. It is reported that this type of cinnamon extract disrupted AB oligomerization and plaque formation in mouse models of AD, followed by improved cognitive abilities.[28,33] Also, when given concomitantly with aluminum in mice, it improved intellectual behaviors and protected the cerebellum from AD-like changes such as AB plaque formation and neural loss, which are usually caused by aluminum if not given with a neuroprotective agent.[34] Furthermore, cinnamon and its polyphenolic constituents interfere with AD progress through suppressing pro-inflammatory

pathways and mediators[35], regulating endothelial integrity and function[36], and probably AD-related epigenetic alterations.[37]

In another study oral feeding of cinnamon powder and sodium benzoate (NaB) suppressed the activation of p21rac geranylgeranyl protein and extenuated oxidative stress in the hippocampus of transgenic mice as evident by decreased dihydroethidium (DHE) and nitrotyrosine staining, reduced homocysteine level and increased level of decreased glutathione. This led to suppression of neuronal apoptosis, inhibition of glial activation, and reduction of Aβ burden in the hippocampus and protection of memory and learning in transgenic mice.[11] In another study by Saeed et al. the potential of CE in memory protection was assessed. It was observed that cinnamaldehyde could improve methamphetamine-induced spatial learning and memory deficits and restore ERK signaling in the rat prefrontal cortex.[38]

It is evident that in AD, the microglia are responsible for excessive production of pro-inflammatory cytokines, hence damaging synaptic connections and resulting in memory impairment. Therefore, maintaining the integrity of synaptic function may halt the progression toward dementia. Regarding this concept, Zhao *et al*.[39] observed the potential anti-inflammatory role of TCA on transgenic mice with induced AD. The results suggested that TCA ameliorated synaptic function in the regions of brain critical for memory process through multiple mechanisms such as, regulating the expression of tau phosphorylation and synaptic proteins, restoring the normal function of an important group of synaptic receptors named N-Methyl-D-aspartate (NMDA) receptors, and suppressing the inflammation process by blocking NF-κB signaling pathway. It has also been shown that TCA improved cognitive impairment and regulated BACE1 (the rate-limiting enzyme for Aβ generation) levels by activating the sirtuin 1 (SIRT1) – peroxisome proliferator-activated receptor gamma (PPARγ) and its coactivator (PGC-1) pathway, reducing Amyloid-β deposition in the brains of Five-month-old 5XFAD mice reducing the symptoms of Alzheimer's and improving the ability to recognize in sick mice.[11] Altogether, CE and in particular, cinnamaldehyde could be used as affordable and safe medications for the treatment and prevention of AD. Moreover, when it comes to the other possible effective substances, Eugenol has also been a promising one. It can be found within cinnamon plant which according to Adefegha *et al*., not only does it have the potential to inhibit acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and monoamine oxidase (MAO) but also in shows a high antioxidant activity.[40]

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder and the most prevalent neurodegenerative movement disorder, characterized by impaired movement accompanied by tremors, stiff muscles, and poor balance. this condition is triggered by the loss of dopaminergic neurons in the substantia nigra (SN) in pars compacta and following lack of adequate dopamine in the striatum.[41] Protein aggregation and the increase of reactive oxygen species (ROS) are found to worsen PD-related complications.[42,43] Regarding difficulties with current treatment approaches, many studies explored the benefits of cinnamon as an anti-PD agent. liver metabolism enables cinnamon to cross the BBB and to have an impact on CNS function.[44] By measuring the effects of cinnamon on mice suffering from PD, Mehraein *et al*.[45], demonstrated that cinnamon and its derivative, cinnamaldehyde, act as potent free radical scavengers and anti-inflammatory agents. These findings suggest that cinnamaldehyde as a natural antioxidant may enhance the survival of dopaminergic neurons in SN. An interesting study conducted by Shaltiel-Karyo *et al*.[46], showed that CE down-regulated the pathways inducing inclusion formation and aggregation of α-Synuclein (α-Syn), a protein associated with Lewy bodies (hallmarks of PD). Furthermore, Patel *et al*.[47] reported the conditional neuroprotective effect of cinnamon and the main product of its liver metabolism, sodium benzoate (NaB), in mice with PD. This effect was only observed in the presence of glial cell-derived neurotrophic factor (GDNF) in astrocytes. GDNF is a strong neurotrophic agent preserving the viability of dopaminergic neurons which its exogenous form should be used with caution in PD patients due to lasting side effects.[48,49] Therefore, the potential benefits of cinnamon may be associated with neurotrophic, light-protective and, anti-inflammatory properties in glial cells. However, high-quality controlled trials are warranted. In addition to the mentioned studies, Kabuto and Yamanushi in 2011 and Moreira Vasconcelos *et al*., in 2020 in two similar studies on 6-hydroxydopamine-induced Parkinson's disease mice models evaluated the efficiency of Eugenol, which is a precise component of Cinnamon, on the treatment of PD. The former study reported the long-term

suppression of epilepiform field potentials and the latter indicated decreased oxidative stress as a result of daily oral administration of Eugenol. Therefore, the consumption of cinnamon can be promising, despite some adverse effects was reported in the Kabuto and Yamanushi's study.[50,51]

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune condition of the central nervous system (CNS) with no definitive treatment, in which myelin components are specifically targeted by the immune system, leading to the decomposition of axonal myelin and associated incapacitating symptoms. Although the blood-brain barrier (BBB) protects CNS from the immune system, immune cells are still able to infiltrate CNS and trigger neurological autoimmune disorders.[52] Cinnamon has shown to be useful for treatment purposes in a variety of immune system activation disorders such as osteoarthritis, cough, hoarseness, sore throat[10,54,55], considering previous findings, several studies measured the effects of this natural product and its bioactives on some crucial factors for the pathogenesis of demyelination in MS mice, including the drastic decrease of regulatory T cells (Tregs)[10,11], widespread inflammation specifically if induced by glial cells[56,57], autoimmune Th1 and Th17 cell hyperactivity[10,55,58], failure of BBB and blood-spinal cord barrier (BSB)[10,59], and the deficiency of neuroprotective agents in CNS.[60] According to their results, cinnamon treatment attenuated these factors through various mechanisms. Interestingly, Brahmachari *et al*.[57] reported that NaB is capable of inhibiting the production of pro-inflammatory molecules by blocking cholesterol-synthesis pathways and reducing activation in cultured astrocytes and microglia, which suggest an indirect role of NaB in reducing cholesterol levels. In addition to in vitro outcomes, NaB suppressed iNOS and IL-1β expression in the cerebellum and spinal cord of experimental allergic encephalomyelitis (EAE) mice, the animal model of MS, suggesting that cinnamon could reduce CNS inflammation in mice.[57] Taken together, the effect of cinnamon and its metabolites on neuroinflammation can explain observed improvements in the treatment of MS and other neurodegenerative disorders including AD and PD.

MIGRAINE

Migraine is a common type of headache with symptoms such as nausea, vomiting, photophobia and, hearing loss, which are heightened with physical activity.[61] Studies have shown that cinnamon can significantly reduce the frequency, severity and, period of migraine attacks, suggesting that cinnamon could be used as an effective clinical treatment for migraine.[62] Also, Cinnamon can reduce obesity, which is associated with an increased risk of migraine.[63,64] Zareie *et al*.[64] performed a 60-day experimental study on 50 eligible patients. During the mentioned period, cinnamon capsules containing 600 mg of cinnamon peel powder and 100 mg of corn starch were prescribed three times a day for the intervention group and 100 mg of corn starch for the placebo group, with the same taste and smell. These capsules were used as an adjunct treatment, meaning that conventional medication in migraine patients continued. After two months, a decrease in headache attacks was seen in both groups, however, this decrease was significantly greater in the intervention group. Also, further assessments showed that headache daily result and disability significantly improved in the cinnamon group compared to placebo. Thus, cinnamon can be prescribed as a supplementary medication for migraine. Figure 1 summarizes the therapeutic effect of cinnamon in neurological disorders.

CONCLUSION

Altogether, antioxidant and anti-inflammatory properties of phytochemical constituents enable cinnamon to be applied as a safe preventive and therapeutic agent against neurological disorders such as neuroinflammation, brain injury, ADHD, AD, PD, MS, and migraine (Table 1.) The cinnamon ingredients such as TCA, cinnamaldehyde as well as, eugenol may also exert several neuroprotective effects. The eugenol is found to be neuroprotective with possible application to treatment of Alzheimers disease, depression, and Parkinsons disease. TCA is known to safely reduce inflammation in microglia, neural damage, apop-tosis, myelin degeneration, dysfunctional protein aggregation, and overall function of the nervous system. No side effects have been reported in the included studies on the cinnamon's application in neurological disorders. Further research is still required to elucidate the mechanisms, molecular pathways, and its potential side effects facilitating cinnamon use as a novel compound in the treatment of neurological disorders.

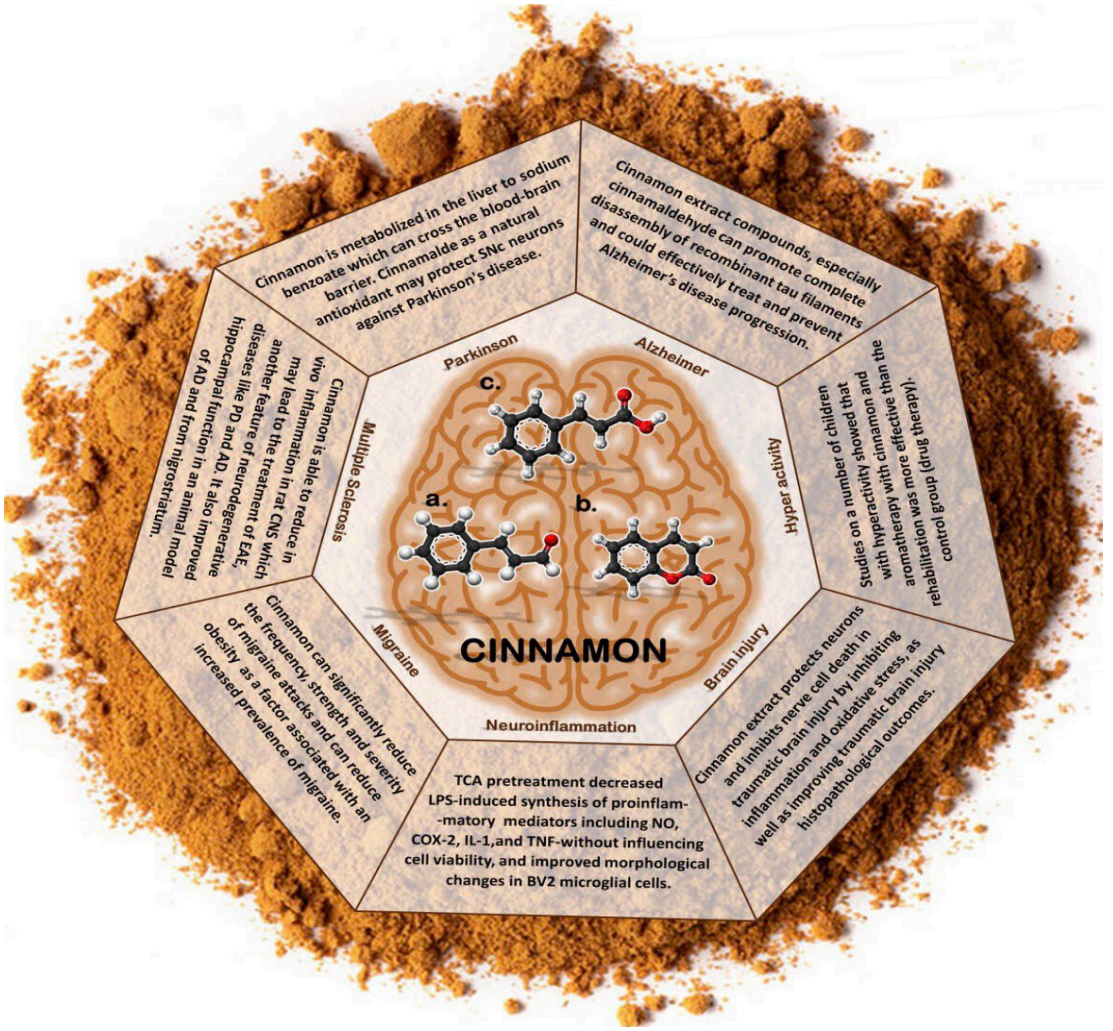

Figure 1. Cinnamon's active ingredients have shown efficiency through various mechanisms in the treatment of Parkinson's disease, neuroinflammation, brain injury, multiple sclerosis, Alzheimer's disease, hyperactivity and migraine. (a. Cinnamaldehyde, b. Coumarin, c. Cinnamic)
Abbreviations: LPS (lipopolysaccharide), TCA (trans-cinnamaldehyde), NO (nitric oxide), COX-2 (cyclooxygenase-2), TNF (Tumor necrosis factor), BV-2 (microglial cells), EAE (Experimental Allergic Encephalomyelitis), SNc (Nigra pars compacta), CNS (central nervous system), AD (Alzheimer's disease), PD (Parkinson's disease).

Table 1: Studies reporting the therapeutic potential of cinnamon for neurological disorders

Author	Year	Neurological disorder	Model	Dose of Cinnamon Or its Constituents	Duration	Outcome
Maiolo *et al.*[65]	2018	PD	In vitro: TH1 transfected SH-SY5Y cells	0-0.5-1-5-10 µM of Curcumin 1-10-100 nM and 1µM of Cinnamaldehyde	24 hours	Cinnamon constituents reduced the toxicity induced by H2O2 but were unable to prevent apoptosis in cells affected by rotenone.
Rao *et al.*[66]	2016	PD	In vivo: Adult male flies (Oregon K)	10-25 µM of cinnamon and its bio-actives (cumin and cinnamaldehyde)	7 days	Cinnamon bioactive substances protect cells from ROT-mediated neurotoxicity as prophylaxis and treatment, which might be vastly due to the antioxidant and neuromodulatory activities of bio-actives.
Kalia *et al.*[67]	2019	PD	A 71-year-old female subject diagnosed with PD	¼ teaspoon of powdered cinnamon and ½ teaspoon of honey	twice a day for 8 weeks	Combined therapy increased on-time and decrease of off-time. Thus, Cinnamon can act as a neuroprotective and anti-inflammatory agent and improve the effectiveness of commonly used anti-PD drugs.
Mansouri *et al.*[68]	2018	PD	In vivo: 70 adult male mice (Wistar) weighing 2.30 g	100-200-400-600 mg/kg of CE	every 48 hours for 20 days	Cinnamon alleviated catalepsy in male mice models of PD, which might be due to the effects of antioxidant substances as well as flavonoids present in cinnamon.
Mehraein *et al.*[45]	2017	PD	In vivo: 45 adult male mice with an average weight of 25-35 g	20-40 mg/kg of CE, 30 mg/kg of cinnamaldehyde (pretreatment and treatment)	2 weeks	Cinnamon water-soluble extract and cinnamaldehyde elevated the performance of MPTP-lesioned mice in the rotarod test and inhibited the deterioration of SNs dopaminergic neurons. thus, cinnamon may act as a neuroprotective agent against PD toxicity.

Kabuto and Yamanushi.[50]	2011	PD	In vivo: 6-hydroxydopamine-induced Parkinson's disease mice models	Oral administration of Eugenol/Zingerone (Daily) + intraperitoneal injection of L-Dopa → Following 1 dose of 6-OHDA injection	Two weeks	Eugenol and Zingerone decreased the striatal DA and its metabolites. Some adverse effects were reported. Therefore, patients should use the mentioned substances cautiously.
Moreira Vasconcelos *et al*.[51]	2020	PD	In vivo: 6-hydroxydopamine-induced Parkinson's disease mice models	Oral administration of Eugenol, Levodopa, or both	Two weeks	Eugenol decreased the oxidative stress and behavioral disturbances induced by 6-hydroxydopamine. The combination therapy was significantly more promising.
Chen *et al*.[69]	2008	ADHD	In vivo: 20 patients with ADHD including 4 girls and 16 boys (ages 2_7 years)	1g of cinnamon 1% in 100 ml of water (inhalation through the nose)	6 months, twice a week, for 30 minutes each time	Children who received CE aromatherapy showed fewer symptoms of ADHD compared to the control group.
Yulug *et al*.[23]	2018	Traumatic Brain Injury	In vivo: Twenty-eight C57BL/6 male mice weighing 25-30 gr	10 mg/kg of Cinnamon Polyphenol extract	30 minutes after the onset of induced injury	Cinnamon polyphenol extract reduced the occurrence of post-traumatic edema and infarct in brain tissue, probably through regulating oxidative stress and inflammatory biomarkers and such as NF-κB, Nrf2, GFAP.
Qubty *et al*.[24]	2020	Traumatic Brain Injury	In vivo: ICR male mice (6-8 weeks and weighing 30-40gr)	10μg/ml of CE	3 weeks	Ingesting CE before and after traumatic brain injury improved post-traumatic memory problems and increased neuronal cell viability in the temporal cortex and the dentate gyrus.
Bektaşoğlu *et al*.[70]	2021	Traumatic Brain Injury	In vivo: thirty-five adult male Wistar albino rats weighing 250-400 g	100 mg/kg of cinnamaldehyde	24 hours	Cinnamaldehyde limited neutrophil accession, repressed reactive oxygen species, decreased histologic damage and hippocampal dysfunction.

Fu *et al*.[8]	2017	Neuro-inflammation	in vitro: The immortalized BV2 murine microglial cell line rat pheochromocytoma PC12 neuronal cell line	0-0.63-1.25-2.5-5-10 μM of TCA before LPS stimulation	2 hours	TCA exerted neuroprotective activity against LPS-induced inflammation in microglia and reversed morphological changes via inhibiting NO production and the expression of COX-2, iNOS, and IL-1β and suppressing NF-κB signaling pathway.
Ho *et al*[9]	2013	Neuro-inflammation	in vitro: LPS activated BV2 microglia culture system	50 mg/ml of CE 100 μM of pure cinnamon compounds after LPS stimulation	1-6-12 hours	Cinnamon ameliorated LPS-mediated inflammation in microglia mainly through preventing NF-κB activation and also by inhibiting NO production and the expression of COX-2, iNOS, and IL-1β.
Schink *et al*.[16]	2018	Neuro-inflammation	in vitro: cultured THP-1 monocyte-macrophage cell line TIB-202(ATCC) HEK-Blue hTLR2 cell line (HEK-TLR2) and HEK-Blue hTLR4 cell line (HEK-TLR4)	4 mg/ml of CE compounds 10-100 ng/ml and 1-10-100-250 μg/ml of p-cymene 10-25-50 μg/ml of TCA	2 hours 2 hours	TCA and p-cymene showed significant anti-inflammatory effects independently and in a synergistic manner as they reduced LPS-induced Akt and IκBα phosphorylation and IL-8 secretion. TCA also inhibited TLR-2 and 4 activations.
Abou El-ezz *et al*.[19]	2018	Neuro-inflammation	in vivo: adult Swiss albino male mice weighing 25-30 g, 3-4 months old	50 mg/kg of TCA	3 hours after a single dose of LPS-injection, continued for 7 days	Cinnamon improved the memory function of mice, via several mechanisms including up-regulating antioxidant enzymes (SOD and GST), activating the Nrf2 signaling pathway, inhibiting the formation of pro-apoptosis and oxidative stress factors (IL-1β, MDA, and caspase-3), and impeding Aβ1-42 aggregation.

Chen *et al*.[20]	2016	Neuro-inflammation	In vivo: adult male C57BL/6 mice (weight 22-28 g) In vitro: Murine BV-2 microglial cells	10-20-30 mg/kg of TCA in vivo 12.5- 25- 50 μM of TCA in vitro	In vivo: 1 hour before I/R In vitro: 15 minutes and 4-12-24 hours	TCA down-regulated the expression of iNOS and COX-2 proteins and reduced the infarcted area in vivo. also, BV-2 microglial cells, LPS-induced cellular changes such as enhanced NO production and NF-κB activation as well as decreased levels of P53 proteins and cytosolic IκBα reversed after TCA administration.
Frydman-Marom *et al*.[71]	2012	AD	In vitro: rat neuronal PC12 cell line In vivo: transgenic *Drosophila melanogaster* model expressing the human Ab42 protein	In vitro:1–100 μg/ml of *CEppt with different CEppt: Aβ 42 concentration ratio In vivo: 0.75 mg/mL of CEppt	24 hours Beginning of larva stage through adulthood	oral consumption of CEppt inhibited β-Amyloid aggregation and improved cognitive performance in mice subjected to AD.
Peterson *et al*.[31]	2009	AD	-In vitro: Tau human isoform(4RL) and residues -Primary hippocampal cells of 18 embryos of Sprague-Dawley rats	0.11-0.22 mg/ml of CE 0-25-50-100μM of proanthocyanidins 0-50-100μM of cinnamaldehyde 0.2 mg/ml of CE 200 μM of proanthocyanidins 100 μM of cinnamaldehyde	3 days 24 hours	CE inhibited Tau accumulation without damaging physiological Tau function. This ability was mainly due to the presence of proanthocyanidins and to a lesser extent, due to cinnamaldehyde.
Tuloeghamar *et al*.[29]	2017	AD	30 male Wistar rats	125 mg/kg of CEextract; 125mg/ kg	4 days	CE ameliorated cognitive impairment caused by STZ in rats.

Irie Y.[72]	2006	AD Depression PD Memory impairment	In vitro: cell death of rat PC-12 cells in culture In vivo: CD-1 mice In vivo: c57B1/6 mice (unpublished data) In vivo: mice microinjected with 750 pmol of Aβ 1-42 (dissolved in saline)	1 μM of eugenol 30 mg/kg B.W./day of eugenol 3 mg/kg B.W./day of FA 100 mg/kg B.W./day of eugenol	24 hours 14 days 24 hours 7 days	Eugenol prevented Aβ-indused extreme invasion of calcium ion into neurons. Eugenol increased expression of brain-derived neurotrophic factor (BDNF) gene in the hippocampus, inhibited monoamine oxidase A (MAO-A). FA repressed gene expression of serum- and glucocorticoid regulated kinase (sgk) gene. Eugenol simplified physiological function that cause amelioration of memory.
Do *et al.*[73]	2020	AD	In vivo: Five-month-old 5XFAD mice	30 mg/kg trans-cinnamaldehyde daily	for 8 weeks	Trans-cinnamaldehyde reduces and regulates BACE1 levels by activating the S sirtuin 1 (SIRT1) – peroxisome proliferator-activated receptor gamma (PPARγ) and its coactivator (PGC-1) pathway, reducing Amyloid-β deposition in the brain of mice with Alzheimer's disease. In this way, it reduces the symptoms of Alzheimer's and improves the ability to recognize in sick mice.
Yulug *et al.*[7]	2019		In vivo: mice	10 mg/kg cinnamon	30 minutes after applying the trauma model	Cinnamon has a neuroprotective role in suppressing inflammation and has been suggested to improve cognition in neurological disorders. It also improves the side effects of traumatic brain injury.

Modi *et al*.[11]	2015	AD	AD (with brain trauma)	100 mg/kg cinnamon powder 50 mg/kg NaB	daily for 2 months	Cinnamon and its metabolite sodium benzoate reduce the effects of neurological disorders. In this way, by affecting oxidative stress and active oxygen species caused by Alzheimer's, it reduces Iba_1 and homocysteine and also inhibits the activation of $p21^{rac}$ in the hippocampus of infected people and suppresses cell apoptosis in the nerves. Caspase 3 levels are also reduced with this substance.
Adefegha *et al*.[40]	2020	AD	In vitro	Measuring the interaction between Eugenol (dissolved in ethanol) with (AChE), (BChE), and (MAO)	-	Eugenol inhibited AChE, BChE, and MAO activities dose-dependently. Additionally, it showed a high antioxidant potential. Thus, Eugenol can be a promising food additive and neuromodulator in AD management.
George *et al*.[32]	2013	AD	In vitro: Tau 187 consisting of aa residues 255–441 of tau 4RL	Cinnamaldehyde 11-40-110-400 μM Epicatechin 100-110 μM	1-24hours 15 minutes 1-24hours	Cinnamaldehyde and epicatechin interfered with tau aggregation without harming its biological function via forming the reversible bound with tau's cysteines. Also, these compounds protected tau from oxidative damage caused by ROS and highly reactive byproducts.
Zhao *et al*.[39]	2019	AD	In vivo: the presenilin 1 and 2 conditional double knockout (PS cDKO) mice	240 ppm of TCA	90 days	TCA restore NMDA receptor function and memory performance via suppressing NF-κB pathway In subjected mice.
Mustafa *et al*.[34]	2020	Aluminum-induced AD	In vivo: 40 adult male albino rats	daily dose of oral TCA: 200 μg/kg/body weight	60 days	TCA improved cognitive performance and showed neuroprotective activity against AD-like changes such as neural loss and AB plaque formation, which were caused by injected aluminum.

Saeed *et al*.[74]	2018	Memory impairment	In vivo: seven groups of six male Wistar rats, weighing 200-250 mg	20/40/or 80 mg/kg of cinnamaldehyde	7 days	Cinnamaldehyde repaired cognitive performance through the ERK pathway and decreased the phosphorylation of ERK1/2 in the prefrontal cortex.
Mondal *et al*.[10]	2015	MS	In vivo: female PLP-TCR transgenic mice female SJL/J mice male C57/BL6 mice all induced with EAE	100 μL	once daily	Ingestion of cinnamon improved symptoms of flared-up/remission and chronic EAE decreased perivascular cuff formation in a dose-dependent manner, maintained Treg cells function via inhibiting NO formation, preserved BBB and BSB integrity, and suppressed neuroinflammation and demyelination.
Zareie *et al*.[64]	2020	Migraine	50 Migraine patients randomized into two groups: cinnamon group and control group	3 capsules per day each containing 600 mg of cinnamon or 3 placebo capsules per day each containing 100 mg of corn starch	Two months	Cinnamon decreased the level of inflammatory mediators such as NO and IL-6, besides, migraine attacks were less frequent and severe and lasted for a shorter period in the cinnamon-treated group.
Muller *et al*.[75]	2006	Epilepsy and headache	A review of the literature on the effects of Eugenol (an aromatic in Cinnamon)	-	-	Eugenol may have the potential therapeutic effect on epilepsy and cephalic pain. This is due to the long-term suppression of epileptiform field potentials which is as a result of the inhibition of synaptic transmission.
Sohrabi *et al*.[76]	2017	Depression and Anxiety	in vivo: Male albino mice (20–30 g)	0.5-1-2 mg/kg of cinnamon essential oil	Acute: 1-8-24 hours Sub-acute: 14 days	Cinnamon essential oil showed anti-depressive and anti-anxiety activities such as shortening the time of immobility in depression assessment tests. Therefore, it may be useful to apply cinnamon in addition to conventional medication.

Abbreviations:
Aβ (Amyloid beta); AD (Alzheimer's Disease); Acetylcholinesterase (AChE); ADHD (Attention Deficit Hyperactivity Disorder); Akt (protein kinase B); BBB (blood-brain barrier); BSB (blood-spinal cord barrier); CAT (Catalase); CD (Conduct Disorder); CE (Cinnamon extract); CNS (Central Nervous System); COX-2 (Cyclooxygenase-2); (3,4-Dihydroxyphenyl)-L-alanine (L-DOPA); Dopamine (DA); Dimethylsulfoxide (DMSO); EAE (Experimental Allergic Encephalomyelitis); GDNF (Glial cell-derived neurotrophic factor); GFAP (Glial Fibrillary Acidic Protein); IL-1β (Interleukin 1 beta); IL-6 (Interleukin 6); IL-8 (Interleukin 8); IκBα (inhibitor alpha); iNOS (inducible Nitric Oxide Synthase); LPS (Lipopolysaccharide); MDA (Malondialdehyde); MS (Multiple Sclerosis); NF-κB (nuclear factor kappa B); NMDA (N-Methyl-D-aspartate); NO (Nitric Oxide); Nrf2 (Nuclear Factor Erythroid 2-related Factor 2); P53 (tumor protein 53); PD (Parkinson's Disease); SOD (Superoxide Dismutase); STZ (Streptozotocin); TCA (trans-cinnamaldehyde); TLR2 (Toll-like Receptor 2); TLR4 (Toll-like Receptor 4); NF-κB(Nuclear Factor kappa B)
*CEppt: a natural substance, based on cinnamon extract

DISCLOSURE

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