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NEUROPROTECTIVE POTENTIAL OF CINNAMON: EVIDENCE FROM ANIMAL MODELS, MECHANISTIC INSIGHTS, AND THERAPEUTIC IMPLICATIONS

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ABSTRACT: Owing to the abundant evidence in preclinical models, Cinnamon, and its bioactive constituents are being explored currently for their preventative and therapeutic potential against select neurodegenerative conditions. Cinnamon contains a wide variety of bioactive components *viz*., cinnamaldehyde, eugenol, cinnamic acid, tannin, catechin, proanthocyanidin, monoterpenes, sesquiterpenes, and coumarin. Cinnamon bark powder, its various extracts and selected components have shown promising results in numerous *in-vitro* and *in-vivo* preclinical models. Its efficacy as an antioxidant, anti-inflammatory, and cognitive enhancing properties, and its propensity to modulate several key biochemical and molecular targets in AD, PD, and TBI models has raised considerable interest among researchers who strongly advocate the use of natural compounds to delay /prevent the progression of neurodegenerative conditions. The present review aims to discuss the status of the current data related to the therapeutic propensity of Cinnamon and its derivatives and highlights the need for well-designed clinical trials.

INTRODUCTION: About 250 species of cinnamon have been identified within the genus (*Cinnamomum* spp.), which is a perennial tree of tropical medicine and a member of the Lauraceae family [1, 2]. The Arabic and Hebraic word '*amomon'* is the source of the botanical name 'cinnamomum', which means "fragrant spice plant." However, the Greek term 'kinamon', which means "Arabian spice," is the source of the popular name cinnamon [3]. Only two of the 250 species of the genus Cinnamomum *Cinnamomum verum*, formerly known as *Cinnamomum zeylanicum*, and *Cinnamomum cassia* are widely distributed.

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Since ancient times, cinnamon, a tree of intermediate height (10 to 15 meters), has been utilized as a spice plant in traditional medicine and food preparation all across the world [4]. Common uses for cinnamon include oleoresin, bark sticks, bark powder, bark essential oil, and leaf essential oil. The essential oil of cinnamon has a sweet, spicy, slightly woody, clove-like perfume, and the aroma is highly distinctive [5]. The flavor of cinnamon is warm, spicy, and aromatic. Because of its scent, which can be added to various meals and perfumes, cinnamon is mostly employed in the aroma and essence industries [6].

A wide spectrum of pharmacological effects of cinnamon is widely documented. It contains several polyphenols and bioactive substances like eugenol and cinnamon aldehyde. Numerous Pharma-cological qualities, including anti-inflammatory, anti-diabetic, anti-microbial, and antioxidant ones,

are said to be present. It has been praised as a powerful intervention spice in lowering the risk of several chronic diseases because of these qualities [7]. The anti-inflammatory properties of cinnamon may also help with diseases like multiple sclerosis and aging-related cognitive loss [8]. Numerous preclinical study findings have drawn significant attention in recent decades due to their potential therapeutic application in the treatment of many neurodegenerative disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD) [9, 10]. Cinnamon's bioactive components have been shown to decrease oxidative brain damage, lower neuroinflammation, and alter neurotransmitter activity. Curiously, studies have demonstrated that cinnamon protects against neurotoxicity, increases synaptic plasticity, and improves cognitive performance [11]. Due to the growing body of data in preclinical models indicating cinnamon and its bioactives have important neuroprotective benefits, numerous researchers are investigating their potential as a treatment for specific neurodegenerative diseases. The evidence that cinnamon and its bioactive compounds have a broad range of neuroprotective potential in different disease models, as well as their likely method of action and prospective future research directions, is the main focus of this review.

Major Bioactive Molecules, Structure: Cinnamon contains various bioactive compounds that have numerous pharmacological properties. It consists of a variety of resinous compounds, including cinnamaldehyde (CA), trans-cinnamaldehyde (TCA), cinnamic acid, and numerous essential oils [12]. A wide range of components in cinnamon essential oils includes CA, Eugenol, Cinnamyl acetate, Linalool, Cinnamic acid, Benzyl benzoate, Coumarin, vanillin, Camphor, *etc* [13, 7]. The major constituents of cinnamon bark oil reported are: Trans-cinnmaldehyde (TCA 91.56%); Cinnamylacetate (1.72%); Eucalyptol (1.26%); Cis cinnamaldehyde (1.28%); Coumarin (0/72%); α-Muurolene (0.72); and α-Cubebene (0.46%). The bioactive chemicals in cinnamon have been separated using a variety of techniques, and the conventional ways of extracting essential oils include steam distillation, hydro distillation, and organic solvent extraction [14]. Although the majority of techniques use solvents like methanol, ethanol, and chloroform [15], new extraction techniques have recently been created using supercritical fluid with the use of microwaves or ultrasounds [16].

Water extraction, however, is the most accessible and safest approach for human health. Using ultra-performance liquid chromatography–high-resolution mass spectrometry (UPLC–HRMS) to profile aqueous cinnamon extract has verified the presence of chemicals such rosavin, camphor, and L (−)-carnitine [17]. Eight ketones, seven monoterpene hydrocarbons, thirty oxidized monoterpenes, four sesquiterpene hydrocarbons, and twenty-three oxidized sesquiterpene hydrocarbons are among these substances [18]. The chemical structures of some important constituents of cinnamon are presented in **Fig. 1.**

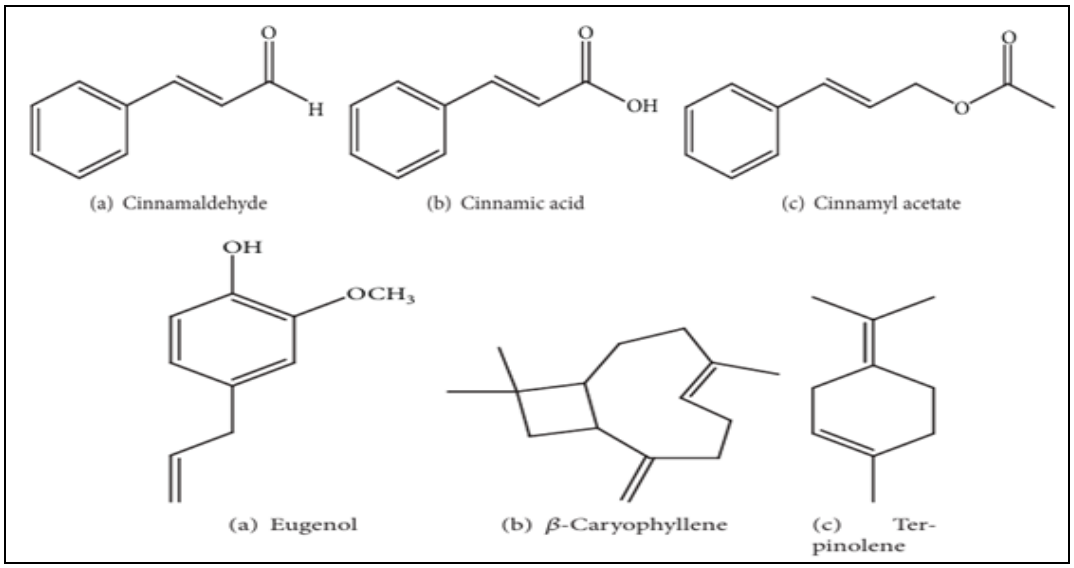

FIG. 1: CINNAMON AND ITS SELECTED BIOACTIVE COMPONENTS

Neuroprotective Propensity of Cinnamon - Multiple Pharmacological Properties: Abundant preclinical evidence has demonstrated the neuroprotective activities of Cinnamon bark and its extracts and major bioactive components in various preclinical models.

Pharmacological Attributes Responsible for Neuroprotection: Cinnamon and its bioactive compounds can exert their potential neuroprotective effects *via* different mechanisms. Three major mechanisms, *viz*., antioxidant, anticholinergic and anti-inflammatory, have been largely explored with cinnamon and bio-actives in various preclinical paradigms. A few salient findings in cell models have been presented in **Table 1.**

TABLE 1: MAJOR EVIDENCE OF NEUROMODULATION IN CELL MODELS

Component/model	Mechanism and Major Effect
Cinnamaldehyde (CA) PC12 cells	Inhibits ROS accumulation, bax expression; enhances Bcl-2 expression; blocks the release of cytochrome c, and decrease the LC3- II/LC3-I ratio ; CA could maintain normal mitochondrial membrane potential and prevent the activation of autophagy [87]
Trans-cinnamaldehyde BV-2 microglial cells (LPS-induced pro-inflammatory response)	Pretreatment significantly inhibited LPS-induced production of NO, expression of iNOS, COX-2, and IL-1β. TCA markedly attenuated microglial activation /neuroinflammation by blocking the NF-κB) signaling pathway [30]
Cinnamalhehyde (CA) TH1 transfected SH-SY5Y cells	Reduced the H_2O_2 induced toxicity induced ; unable to prevent rotenone induced apoptosis [88]
Trans-cinnamaldehyde (TCA) & p-cymene THP-1 monocyte-macrophage cell line TIB-202(ATCC)	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 [89]
Eugenol	Eugenol inhibited AChE, BChE, and MAO activities dose-dependently and showed a high antioxidant potential [90]
trans-cinnamaldehyde (TCA) Murine BV-2 microglial cells	TCA down-regulated the expression of iNOS and COX-2 proteins 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 [32]
Hydro alcoholic extract, cinnamon essential oil, and CA 6-OHDA-exposed PC-12 cells	Increase cell viability, decrease ROS content; decreased cyt-c, increase surviving, reduced P-p44/42/p44/42 to a level near to that of the related control [91]
Cinnamon essential oil (EO) PC-12 cells	Potent activity toward AChE and BChE; showed inhibition against BACE1 (beta-secretase 1); no neuroprotective potential against β-amyloid (Aβ)-induced neurotoxicity [28]
Ethanolic extract of cinnamon (Nano suspension)	Nano suspensions exhibited antioxidant properties [92]

Antioxidant and Anticholinergic Attributes: Currently, spices and medicinal plants have received wide attention as sources of beneficial antioxidants against various diseases, including neurodegenerative disorders [19]. Cinnamon is a potent antioxidant, anticholinergic, and antidiabetic due to its high phenolic content [20]. In a comparative study among 26 spices, cinnamon showed the highest antioxidant activity [21] and its antioxidant potential have been attributed to the presence of various constituents *viz.*, pyrogallol, ferulic acid, and p-coumaric acid in along with p-hydroxybenzoic acid, p-coumaric acid, and pyrogallol in the ethanolic and aqueous extracts. Flavonoids from cinnamon have demonstrated notable antioxidant and free-radical-scavenging capabilities [22].

Repeated oral administration (90 d) of the bark powder of *C. verum* (10%) produced antioxidant activities as indicated by cardiac and hepatic antioxidant enzymes, lipid conjugate dienes, and glutathione [23]. CA and other cinnamon components also have significant inhibitory effects on the expression of inducible nitric oxide (NO) and nitric oxide production [7]. Additionally, the suppression of pyrogallol autoxidation demonstrated that cinnamon oil had superoxide dismutase (SOD)-like action [24]. Remarkably, when compared to the natural antioxidant *α*-tocopherol, both ethanolic and hot water extracts of the dry bark of *C. cassia* demonstrated greater antioxidant activity *in-vivo* [25]. Cinnamon is extensively studied for its anti-cholinesterase (AChE) activity. The essential oil (EO) of *Cinnamomum verum* demonstrated

antioxidant activity, as evidenced by its ability to scavenge free radicals as well as reduce ferric ions [26]. Employing an *in-silico* approach, Syarafina *et al.,* [27] screened 60 bioactive compounds from cinnamon bark to identify potential AChE inhibitors. 12 out of 15 tested ligands showed potential as AChE inhibitors, with epicatechin and medioresinol demonstrating the highest affinity, comparable to the natural ligand donepezil. Another study [28] also demonstrated that cinnamon EO) exhibited good inhibitory activity against both AChE and butyrylcholinesterase (BChE), and also against BACE1 enzyme, a key enzyme in the production of amyloid-beta, a protein that forms plaques in the brains of AD patients. Molecular docking simulations have also suggested that compounds such as Coumarin, Piperonal, Cinnamaldehyde dimethyl, and alpha-Copaene could potentially inhibit human AChE.

Anti-inflammatory Effects: Cinnamon constituents are known to inhibit neuro-inflammation as evidenced by both *in-vitro* and *in-vivo* studies. Predominantly, these actions are mediated by the antioxidant and free radical scavenging activities of cinnamon constituents. CA is the most effective anti-neuroinflammatory compound in cinnamon extract [29].

In neurodegenerative conditions like AD and PD, microglial activation contributes to neuro-inflammation and neuronal death. If neuro-inflammation is managed, outcomes of neurodegenerative diseases may be improved. In lipopolysaccride-activated BV2 microglia, cinnamon extract dramatically reduced the synthesis and expression of NO, interleukin (IL)-1b, IL-6, and tumour necrosis factor (TNF)-α and Cinnamon's ability to reduce neuroinflammation most likely resulted from blocking the activation of nuclear factor-kB. By inhibiting the nuclear factor kappa B (NF-κB) signaling pathway and reducing neuroinflammation, both TCA and HCA significantly reduced LPS-induced neuronal mortality *in-vitro* [30]. HCA also inhibited neuroinflammatory signaling pathways by targeting low-density lipoprotein receptor-related protein 1 (LRP1), which in turn inhibited NF-κB, extracellular regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p-38 MAPK) [31].

In mice models, TCA was shown to reduce the selective dopaminergic neuronal death that occurred in the *Substantia nigra* of 1,1,1,2-,3,6,-tetrahydropyridine (MPTP) mice models as evidenced by the attenuation of the MPTP-mediated stimulation of LC3 puncta, a microtubule-associated protein. In the same model, CA treatment increased downregulated p62 in the *Substantia nigra* of MPTP mice. These findings suggest that CA has neuroprotective effects in PD models [32]. Further, Cinnamic aldehyde blocks the autophagy of the neuronal cells from the toxic effect of 1-methyl-4-phenyl-1,2,3,6- tetrahydro-pyridine by stopping the stimulation pf microtubule associated protein light chain 3 (LC3) and enhanced the down regulation of p62 there by blocking the autophagy inhibitors in PD models [33].

Numerous researchers have explored the anti-inflammatory potential of TCA. TCA markedly reduced inflammation in microglia, neural damage, apoptosis, myelin degeneration [30, 29, 34], dysfunctional protein aggregation, and overall function of the nervous system [35, 11]. In mice with neuroinflammation, TCA reduced memory impairment *via* reducing microglial activation by disrupting NO synthase mRNA [36]. It dramatically decreased the production of NO and ROS [37]. TCA therapy restored tau-protein hyperphosphorylation and aberrant synaptic protein expression in the hippocampus and prefrontal cortex of PS cDKO double knockout mice. Importantly, TCA's interrupting effect NFκB signaling pathway resulted in the regulation of neuroinflammatory responses, which improved NMDA receptor dysfunction and memory deficits in PS cDKO mice [38].

The neuroprotective effects of Cinnamon bio-actives were also studied in traumatic brain injury (TBI) models. TBI can seriously impair brain function and cause several ischemic pathologic changes in the brain. CA demonstrated neuroprotective effects by limiting neutrophil recruitment, lowering ROS levels, minimizing histologic damage, and alleviating acute hippocampal dysfunction [39]. Interestingly, administering cinnamon polyphenol extract has also demonstrated notable neuroprotective effects in TBI situations [40]. Malondialdehyde, superoxide dismutase, glutathione peroxidase, and other

oxidative parameters, as well as inflammatory markers like NF-kB, interleukin 1-beta, interleukin 6, nuclear factor erythroid 2-related factor 2, glial fibrillary acidic protein, and neural cell adhesion molecule, were all significantly altered in this model. The extract also significantly reduced the formation of infarct and edema in this model. Many substances present in cinnamon essential oil, including as TCA, caryophyllene oxide, eugenol, and cinnamonyl acetate, demonstrated exceptional anti-inflammatory qualities by lowering the production of NO by macrophages stimulated by lipopolysaccharide. Additionally, several other pieces of evidence in animal disease models suggest its usage as a safe preventive and therapeutic agent against neurological illnesses such migraine, attention deficit hyperactivity disorder, AD, PD and neuroinflammation.

Antidepressant Potential of Cinnamon: The efficacy of cinnamon bark, different extracts, and cinnamon oil to mitigate depression associated biochemical processes has been well demonstrated. Phenols generated from cinnamon can counteract oxidants that result in oxidative stress, which lowers the incidence of inflammatory activity in brain neuron cells. A recent study found that the phenols in cinnamon extract effectively reduced the action of TNF-α, a pro-inflammatory cytokine, in the hippocampus and neuron cells, restoring optimum and elevating serotonin levels in the brain [41]. In the past, it was demonstrated that sodium benzoate, a metabolite of cinnamonaldehyde, increased BDNF activity, which is involved in the stimulation of dopamine receptor expression [42]. Further, mice treated with a hydroalcoholic extract of cinnamon (*C. verum*) showed significant anti-depressant and anti-anxiety benefits in a lead acetate paradigm [43].

Using various behavioral tests, a recent study showed how inhaling cinnamon essential oil (CIEO) affected mice behavior [44]. Anxiolytic effects and improved social conduct were demonstrated by CIEO inhalation. Microarray investigation of the hippocampus after CIEO therapy showed overexpression (15 genes) and downregulation (17 genes). Interestingly, the most important genes among them that are engaged in biological pathways and processes connected to anxiety, such as the control of neuroinflammation and neuronal death, are Dcc, Egr 2, and Fos. Similarly, it was demonstrated that cinnamal-dehyde, the primary ingredient in CIEO, significantly improved the recovery of MK-801-induced anxiety-related alterations in a zebrafish model, as demonstrated by the electro-encephalogram power spectrum.

In mouse models, a standardized methanolic extract of *C. cassia* bark was evaluated for antidepressant activity using various behavioral tests such as the tail suspension test (TST), forced swim test (FST), and locomotor activity test. The *C. cassia* extract significantly decreased the immobility time in TST, increased 5-hydroxytryptophan (5-HTP) -induced tremors that led the authors to speculate that the serotonergic system is most likely involved [45]. Similar studies with aqueous extract of cinnamon (*C. verum*) bark showed an antidepressant-like effect among mice exposed to open-space forced swim test (OSFST), and failed to significantly affect non-spatial short-term memory and locomotor activity of the mice subjected to NORT (Novel Object Recognition Test) and OFT (Open Field Test), respectively [46]. Intraperitoneal administration of cinnamon essential oil significantly decreased the immobility time of both FST and TST as compared to the control group of mice [47]. Based on these results, the researchers attributed this potential to trans-cinnamaldehyde, and suggested that cinnamon essential oil may serve as an adjunctive therapy in improving symptoms of depressive and anxiety disorders.

In rat models of depression, few studies have also documented the antidepressant efficacy of Cinnamon (*C. burmannii*) bark extract (CE) employing chronic mild stress induced (CMS) models [48]. Study showed that CE could reduce the immobility when compared to the CMS group. Interestingly, improved serotonin levels in the hippocampus were accompanied with increased expression of TNF-α expression as a marker of inflammation had increased in the CMS group. Another study, showed that hydroalcoholic extract of Cinnamon (HEC) significantly attenuated the immobility time, was significantly increased in the depressed group [49]. Interestingly, an increase in the BDNF protein and TrkB gene expression levels were also evident in the prefrontal cortex of the treatment groups.

The potential of CA to influence the intergenerational inheritance of depression in mice models of depression generated by chronic moderate stress (CMS) and paternal stress exposure-induced elevated corticosterone (CORT) [50]. According to this study, co-administration of CA to F0 males protected the F1 male offspring from exhibiting depressive-like traits. Additionally, CA dramatically improved the depressive-like behaviors of F1 offspring born to CMS mice that were triggered by chronic variable stress (CVS). Increased miR-190b expression was associated with decreased BDNF and GR in the hippocampus of F1 males of CORT-or CMS-induced depressive-like animals; these effects were mitigated by CA. In an interesting approach, a recent investigation explored the effects and mechanisms of Cinnamon Oil Solid Self-Micro emulsifying Drug Delivery System (CO-S-SME) in a chronic unpredictable mild stress (CUMS)-induced mouse model (51). According to behavioral tests, CO-S-SME may successfully alleviate depressive-like behaviors in CUMS mice, as demonstrated by elevated neurotransmitter levels and decreased corticosteroid and inflammatory factor expressions. Based on these findings, CO-S-SME may be an effective antidepressant that acts through CORT, inflammatory cytokines, and monoamine neurotransmitters. (Please refer **Table 3B**).

Cognitive Enhancing Potential of Cinnamon: Evidence gathered both *in-vitro* and *in-vivo* has demonstrated the cognitive enhancing potential of cinnamon and its components as reviewed recently [8]. Several *in-vitro* studies have reported a positive impact on cognitive function in models. A methanol extract of cinnamon bark inhibited Aβ40 production in APP-CHO cells [52], while cinnamaldehyde inhibited Aβ aggregation and increased cell viability in APP (amyloid precursor protein) and APPsw cell lines [53]. Studies reported that trans-cinnamaldehyde reduced neural death in microglial and neuronal cell lines [30], and cinnamaldehyde significantly reversed Aβ neurotoxicity in SH-SY5Y neuroblastoma cells [54] (refer to **Tables 2** and **4A)**.

Following the injection of cinnamon components, multiple *in-vivo* studies have also demonstrated considerable beneficial outcomes revealing the cognitive benefits, which are consistent with various *in-vitro* findings. Nevertheless, the discrepancies found in these investigations can be attributed to changes in the types of behavioral tests performed, the routes and durations taken, and quantities of cinnamon components supplied. Additionally, because of its general activities as an antioxidant, an inhibitor of amyloid plaque, and an anti-acetylcholinesterase, eugenol has cognitive protective properties. There is evidence that both CA and TCA enhance insulin and NO signaling and provide protection against cognitive decline.

A controlled cortical impact (CCI)-induced preclinical mouse model of traumatic brain injury (TBI) was used to test NaB to investigate the potential therapeutic effectiveness of cinnamon metabolite [55]. It has been demonstrated that oral administration of NaB reduces microglia and astrocyte activation and inhibits the production of inducible iNOS in the cortex and hippocampal regions of mice exposed to CCI. Additionally, NaB lowered the size of the lesion cavity and vascular damage in the brain among mice with CCI. Mice treated with NaB exhibited a significant decrease in depressive-like behaviors as well as notable improvements in memory and locomotor abilities. Likewise, in rats with TBI, phosphate buffer extract (CE) of cinnamon bark virtually eliminated memory loss and reduced neuronal loss [56]. There were no appreciable variations in anxiety or motor activity, and CE consumption reduced neuronal loss in the dentate gyrus and temporal cortex. These results have demonstrated a novel therapy strategy to enhance cognitive performance and lessen memory loss in TBI patients.

Preclinical Evidence in Animal Models:

Evidence in Invertebrate Models: Studies of cinnamon constituents on neuromodulatory potential in invertebrate models have been very promising **Table 2.**

TABLE 2: NEUROMODULATORY EFFECTS OF CINNAMALDEHYDE, CINNAMON EXTRACT IN INVERTEBRATE MODELS

Compound	Model	Result
Cinnamadehyde	Drosophila	Improved the lifespan of both AD and non-AD flies; improved the health span of AD flies overexpressing the Tau protein, but had no positive impact on the health

		span of AD flies overexpressing the Aβ_{42} protein [57]
Cinnamon extract precipitation (CEppt)	Drosophila	On administering to Drosophila fly model expressing mutant A53T α-syn in the nervous system, a significant curative effect on the behavioral symptoms of the flies and on α-syn aggregation in their brain was observed [58]
Cinnamon extract (aqueous)	Drosophila-Rotenone model (ROT)	Protected the flies against ROT-induced mortality; diminished locomotor deficits and significantly abrogated the degree of oxidative impairments; restored ROT-induced mitochondrial dysfunctions [59]
Cinnamon bioactive compounds	Drosophila and C. elegans	Treatment with bioactive compounds caused statistically significant amelioration (12-30%) in markers of neurodegeneration and neurotoxicity both *C. elegans* and *D. melanogaster*[60]
Cinnamaldehyde (CA)	*C. elegans*	CA reduces β-Amyloid toxicity in a *C. elegans* model of Alzheimer's disease; exerts its beneficial effects through mTORC1 and autophagy signaling. CA promotes longevity by inducing a dietary restriction-like state [61]

CA improved the lifespan of both AD and non-AD *Drosophila* and enhanced the health span of Tau-overexpressing AD flies [57]. Cinnamon extract significantly improved behavioral symptoms and α-synuclein aggregation in a *Drosophila* model of PD [58]. ACE cinnamon extract protected *Drosophila* against rotenone-induced mortality, locomotor deficits, and oxidative damage while restoring mitochondrial function [59]. Cinnamon bioactive compounds ameliorated neurodegeneration and neurotoxicity markers in *C. elegans* [60]. In *C. elegans*, cinnamaldehyde reduced β-amyloid toxicity *via* mTORC1 and autophagy signaling, promoting longevity [61].

TABLE 3A: NEUROMODULATORY EFFECTS OF CINNAMON, CINNAMON OIL, AND SODIUM BENZOATE

Trauma model mice	Cinnamon has a neuroprotective role in suppressing inflammation and suggested to improve cognition in neurological disorders. It also improves the side effects of traumatic brain injury [40]
MS (Multiple sclerosis) -	female PLP-TCR transgenic mice, female SJL/J mice, male C57/BL6 mice**,** all induced with EAE: 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 [34]
Depression and Anxiety	Albino mice: Cinnamon essential oil showed anti- depressive and anti-anxiety activities such as shortening the time of immobility in depression assessment tests [47]
Antidepressant	Mice: Behavioral tests - CO-S-SME (Cinnamon Oil Solid Self-Microemulsifying Drug Delivery System) could effectively improve depression-like behaviors; effectively increased neurotransmitter levels and reduced the expressions of corticosterone and inflammatory factors in CUMS (chronic unpredictable mild stress) mice. CO-S-SME also changed the intestinal flora composition, decreased the ratio of Firmicutes to Bacteroidetes, reduced relative abundances of Lactobacillus, modulated Alpha diversity and beta diversity [51]
Lupus model	(Imiquimod-induced) - C57BL/6J female mice: Increased ratios of p NRF2/NRF2 and p-FOXO3/FOXO3 ratios in the hippocampus were alleviated by cinnamon treatment [81]
Transgenic mice (expressing mutant A53T humanα-synucleinopathies), AD-model	A53T mice, NTG mice: Cinnamon reduced α-syn in nigra, hippocampus & brain stem. Improvement in motor and cognitive function by both cinnamon and NaB; Spression of glial cell activation in nigra; upregulation of neuroprotective proteins like DJ-1 and Parkin. Altogether they might halt the progression of α-synnuclenopathies[80]
	5XFAD Transgenic Mice): Cinnamon powder and NaB suppressed the activation of p21^{rac} and attenuated oxidative stress in the hippocampus of Tg mice; accompanied by suppression of neuronal apoptosis, inhibition of glial activation, & reduction of Aβ burden in the hippocampus and protection of memory and learning in transgenic mice [35]

TABLE 3B: EXPERIMENTAL MODELS *(IN-VIVO)* WHICH DEMONSTRATE THE NEURO PROTECTIVE EFFICACY OF CINNAMALDEHYDE (CA)

Traumatic Brain Injury	adult male Wistar rat: CA limited neutrophil accession, repressed reactive oxygen species, decreased histologic damage and hippocampal dysfunction [39]
Memory Impairment	Wistar rats: CA repaired cognitive performance through the ERK pathway and decreased the phosphorylation of ERK1/2 in the prefrontal cortex [67]
Neuroprotective effect	Rat (sciatic nerve crush): CA accelerated sciatic nerve recovery after crush injury; had better impacts on sciatic functional index (SFI) recovery, muscle mass ratio, and myelin content [68]
Mice	biphasic effect of CA on passive avoidance memory (dose- dependency), an improvement on a dosage of 45 mg/kg, 50 mg/kg, 100 mg/kg and memory impairment on a dosage of 12.5-40 mg/kg (passive avoidance memory test) [69]

Evidence in *In-vivo* Disease Models: Salient findings documented in various *in-vivo* models have been summarized in Tables **4A & B**; likewise, selected data on the different extracts of cinnamon are presented in **Table 5.**

TABLE 4A: MAJOR *IN-VIVO* STUDIES DESCRIBING THE NEUROMODULATORY EFFECTS OF TRANS-CINNAMALDEHYDE (TCA)

Neuro Inflammation Adult Swiss albino male mice	TCA 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 [70]
Neuro Inflammation Adult male C57BL/6 mice	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 [32]
AD 5XFAD mice	TCA 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 [64]
AD Conditional double knockout (PS cDKO) mice:	TCA restores NMDA receptor function and memory performance via suppressing NF-κB pathway [38]
Aluminum- induced AD Adult male albino rats	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 [65]
Antidepressant effect – mouse:	TCA (50 mg/kg, po) revealed a significant effect on reduced immobility in the FST, elevated the level of 5-HT and decreased the ratio of Glu/GABA, COX-2, TRPV1 and CB1 protein level in mice hippocampus [66]
AD- 5XFAD Transgenic Mice	TCA led to an improvement in AD pathology by reducing BACE1 levels through the activation of the SIRT1-PGC1α-PPARγpathway [64]

TABLE 4B: *IN-VIVO* STUDIES WITH EUGENOL AND CINNAMIC ACID

Lead-induced memory impairments - Wistar rats:	Lead acetate exacerbated memory impairments in stressed rats and Eugenol improved these impairments [71]
Study on cognition in AD model - Wistar rats:	AD model groups showed a significant positive result on memory (step-through latency), and the histological study showed a positive effect on the reduction of amyloid plaques [72]
Neurogenesis and memory performance – Mice:	Eugenol enhanced putative neural stem cells (NPCs) and granular cells (GC) number, and decreased neuronal cell death in DG; it also increased dendritic complexity of neurons in DG region; in CA1, it has given a positive effect only on the basal area [73]
Transgenic Mice expressing PPARa 5XFAD mice -	Trans cinnamic acid induced lysosomal biogenesis in mouse primary brain cells via upregulation of TFEB remarkably reduced cerebral amyloid-beta plaque burden and improved memory via PPARα. Positive on spatial memory improvement [74]

TABLE 5: *IN-VIVO* STUDIES WITH CINNAMON EXTRACTS

Cognition model - Diabetic rats:	Aqueous Cinnamon extract (ACE) had overall positive effects on avoidance and spatial memory (Y Maze and avoidance memory) [75]
Aluminum -induced AD - Wistar rats:	Progressive improvement in memory and intellectual performance was observed upon ACE administration; played a protective role against Amyloid-Beta formation [65]
TBI by 70-g weight drop TBI device - ICR Mice:	ACE consumption almost completely mitigates memory impairment and decreases neuronal loss after TBI; attenuated neuronal loss in the temporal cortex and the dentate gyrus; Improving in cognition and decrease memory loss, recognition and visual memory (NOR and Y-Maze) [56]
PD - adult male mice:	ACE and cinnamaldehyde elevated the performance of MPTP- lesioned mice in the rotarod test and inhibited the deterioration of SNs dopaminergic neurons [76]
Non-transgenic rat model of AD (NTAD):	ACE Improved the insulin sensitivity, increased phosphorylated glycogen synthase kinase-3β (pGSK3β), inhibited the cholinesterase activity, and improved the learning ability; Histological evaluation revealed an increase in neuron count in the DG sub-field of hippocampus [77]
TBI - C57BL/6 male mice:	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 [40]
AD - Wistar rat:	Cinnamon extract ameliorated cognitive impairment caused by STZ in rats [78]
Formaldehyde (FA) model for cognition function deficit - Wistar rats:	CE improved the rats' Morris water maze performance, decreased the levels of phospho-tau (Thr^{231}), caspase-8, IL-6, and TNF-α, and reduced the ratio of apoptotic to intact neurons. Overall, cinnamon improved cognitive performance in FA-treated rats by eliminating tau hyper phosphorylation, inflammatory cytokines, and nuclear damage [79]

PD and AD Models: Several investigations have shown that cinnamon extracts and NaB have neuro-modulatory actions, which amply support their positive benefits in AD and PD models. It has been found that NaB modulates mevalonate metabolites to upregulate DJ-1(9). In the mouse central nervous system, cinnamon extracts and NaB also increase neurotrophin-3 (NT-3) and neurotropic factors such BDNF [42]. A naturally occurring substance called "CEppt," which was separated from cinnamon extract, dramatically decreased the production of harmful NAβ-amyloid polypeptide (Aβ) oligomers and prevented their toxicity to neuronal PC12 cells. According to the study, CEppt completely eliminated the tetrameric species of Aβ in the brain of the fly model of AD, resolved the reduced immovability, and improved the locomotion deficiencies. This resulted in a discernible decrease in Aβ oligomers, which in turn reduced plaques and enhanced the cognitive function of transgenic mouse models [62]. Two of the primary characteristics of AD, tau aggregation and filament development, may be lessened by the aqueous extract of C. zeylanicum, according to another study. Cinnamon may be used to treat AD since the extract may promote the full fragmentation of recombinant tau filaments and significantly alter the form of paired helical filaments from AD brain [63].

It is generally known that neurotrophic factors, a family of chemicals, maintain the survival of existing neurons while also stimulating and regulating neurogenesis. *In-vivo*, studies have demonstrated that oral administration of ground cinnamon increased BDNF and NT-3 levels in the mouse central nervous system [42]. The expression of BDNF and NT-3 in primary human neurons and astrocytes was also dose-dependently increased by NaB. Its neurotrophic effect through CREB activation was evident from the recruitment of CREB and CREB-binding protein to the BDNF promoter by NaB, the siRNA knockdown of CREB, and the further activation of cAMP Response element binding (CREB) protein [42].

In AD models, TCA reduced amyloid-β deposition by regulating BACE1 through the SIRT1-PGC1α-PPARγ pathway in 5XFAD mice [64]. It also restored NMDA receptor function and memory in PS cDKO mice *via* NF-κB suppression [38] and protected against aluminum-induced AD-like changes in rats [65]. Additionally, TCA exhibited antidepressant effects in mice by modulating serotonin levels and neurotransmitter balance [66].

TBI Model: In a rat TBI model, CA reduced neutrophil infiltration, suppressed ROS, and minimized hippocampal dysfunction [39]. In memory impairment model, CA improved cognitive function through the ERK pathway by decreasing ERK1/2 phosphorylation in the prefrontal cortex [67]. In addition, CA enhanced sciatic nerve recovery after crush injury by improving the sciatic functional index, muscle mass ratio, and myelin content, suggesting its role in nerve regeneration [68]. In mice, CA exhibited a biphasic effect on passive avoidance memory, enhancing memory at doses of 45–100 mg/kg while impairing it at lower doses [69]. In mice models, TCA improved memory by upregulating antioxidant enzymes, activating the Nrf2 pathway, and inhibiting oxidative stress factors (IL-1β, MDA, caspase-3), thereby preventing Aβ1-42 aggregation [70]. In C57BL/6 mice, TCA reduced neuroinflammation by downregulating iNOS and COX-2 while mitigating LPS-induced changes in BV-2 microglial cells [32].

Eugenol improved memory impairments in rats by counteracting the detrimental effects of lead acetate exposure [71]. Data on Eugenol and its protective effects is presented in Table 4 d. In AD model, it enhanced cognition by reducing amyloid plaque deposition, as confirmed by histological and behavioral studies [72]. Moreover, Eugenol promoted neurogenesis and memory performance in mice by increasing neural stem cells in the dentate gyrus while reducing neuronal cell death [73]. Trans-cinnamic acid showed neuroprotective effects in 5XFAD transgenic mice by inducing lysosomal biogenesis through TFEB upregulation. This led to a remarkable reduction in cerebral amyloid-beta plaque burden and improved spatial memory [74].

Cinnamon Extracts: In a trauma model (mice), cinnamon improved cognition and traumatic brain injury symptoms [40] **Table 5**. In multiple sclerosis (MS) models, cinnamon ingestion alleviated symptoms of both acute and chronic experimental autoimmune encephalomyelitis (EAE), preserved blood-brain barrier, reduced neuroinflammation and demyelination [34].

Cinnamon essential oil exhibited antidepressant and anxiolytic properties [47]. Moreover, cinnamon oil-based self-microemulsifying drug delivery system (CO-S-SME) improved depression-like behaviors in mice subjected to chronic unpredictable mild stress (CUMS). It increased neurotransmitter levels, reduced corticosterone and inflammatory factors, and positively altered gut microbiota composition [51].

As presented in **Table 5**, aqueous cinnamon extract (ACE) has shown neuroprotective effects in various cognition-related models**.** In diabetic rats, ACE enhanced spatial and avoidance memory, indicating cognitive benefits [75]. In an aluminum-induced AD rat model, ACE improved memory and intellectual performance while preventing amyloid-beta formation [65]. Consistent with this data, in TBI mice, ACE significantly mitigated memory impairment, preserved neuronal integrity in the temporal cortex and dentate gyrus, and improved cognitive functions [56]. In PD model, ACE and cinnamaldehyde enhanced motor function in MPTP-lesioned mice and protected dopaminergic neurons in the substantia nigra [76]. Also, in AD rat model, ACE improved insulin sensitivity, inhibited cholinesterase activity, and enhanced neuronal survival in the hippocampus [77].

Cinnamon polyphenol extract reduced post-traumatic edema and infarct in C57BL/6 mice with traumatic brain injury (TBI), by modulating oxidative stress and inflammatory markers [40]. In AD models, cinnamon extract (CE) alleviated cognitive impairment in STZ-diabetic rats and enhanced cognitive function in formaldehyde-exposed rats by reducing tau phosphorylation, inflammatory cytokines, and neuronal apoptosis [78, 79]. Furthermore, cinnamon powder and sodium benzoate improved motor and cognitive function in transgenic mice with α-synucleinopathy, reduced α-synuclein accumulation, and upregulated neuroprotective proteins DJ-1 and Parkin [80]. *C.cassia* powder alleviated oxidative stress in the hippocampus of lupus-model mice by increasing p-NRF2/NRF2 and p-FOXO3/FOXO3 ratios [81].

Clinical Evidence: Despite numerous preclinical studies demonstrating the neuroprotective properties of cinnamon in animal models, studies involving human subjects are limited. Two recent studies have been reported. In one of the studies, a 71-year-old female subject diagnosed with PD for more than 15 years, a combined therapy of cinnamon and honey demonstrated clinical improvement in the "on-time" administration along with oral pharmacological medicine [82]. In another study [83], 50 migraine patients who were given three daily 600 mg cinnamon capsules showed reduced inflammatory markers (NO, IL-6), fewer as well as less severe and shorter migraine attacks. These findings highlight cinnamon's therapeutic potential in neurological disorders and inflammation-related conditions. However, specific, well-designed, randomized clinical trials are needed to validate these effects in larger populations.

Bioaccessability/ Bioavailability: Cinnamon is a potential natural pharmaceutical for the treatment of several health issues especially neurological disorders. However, the presence of blood brain barrier, the low bioavailability and fast systemic clearance of cinnamon biactives limit its *in-vivo* activities [84]. Several strategies are employed to enhance the bioavailability of cinnamon and its constituent compounds. Nano formulations and Encapsulation are reported to be the most effective ways in this direction.

Many encapsulation techniques, such as spray drying, coacervation, precipitation, freeze drying, ionic gelation, and ultrasonication, have been used recently to mitigate the limitations and improve the bioavailability of cinnamon bioactives [85, 86]. These methods are frequently used to distribute cinnamon bioactives, guaranteeing regulated release and improving functionality. Additionally, they enhance the solubility and stability of cinnamon's bioactive components even in harsh environmental conditions and protect them from degrading reactions.

Summary and Future Perspective: The cinnamon extracts, their bioactive compounds, and cinnamon oil exhibit significant neuroprotective effects and have been adequately demonstrated in various preclinical studies. Cinnamon alleviates neurodegeneration *via* different molecular mechanisms, involving antioxidant, anti-inflammatory, anti-amyloidogenic, regulation of apoptosis and autophagy-modulating properties **Fig. 2** and **3**.

Mechanistically, cinnamon bio-actives alleviate oxidative stress by enhancing the activity levels of antioxidant enzyme and mitigating ROS. They inhibit neuroinflammation by suppressing microglial activation and pro-inflammatory cytokines. Additionally, cinnamon bio-actives prevent tau aggregation and β-amyloid toxicity, which are crucial hallmarks of AD.

Moreover, cinnamaldehyde modulates autophagy via the mTORC1 pathway, facilitating protein clearance in neurodegenerative disorders. Several studies using *Drosophila*, *C. elegans*, and rodent models have also shown that cinnamon improves lifespan, cognitive function, and locomotor deficits in AD, PD, and rotenone-induced neurodegeneration.

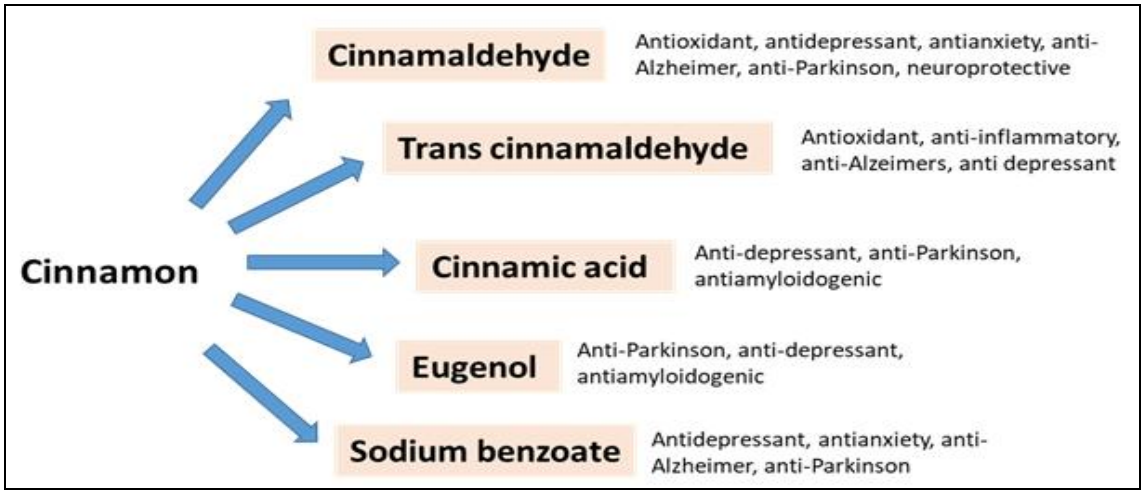

FIG. 2: SCHEME DEPICTING THE DIFFERENT BIOACTIVE COMPONENTS OF CINNAMON AND THEIR PHARMACOLOGICAL PROPERTIES

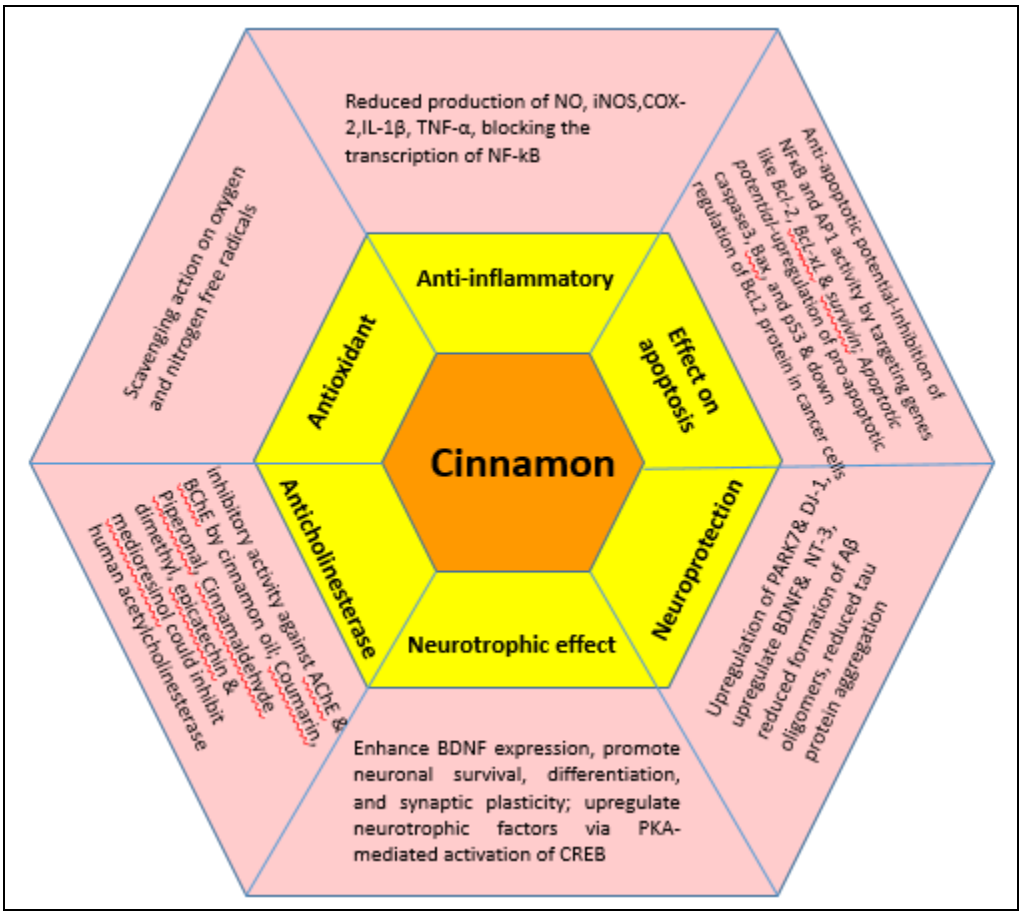

FIG. 3: DIFFERENT MECHANISMS RESPONSIBLE FOR NEURO-MODULATORY POTENTIAL OF CINNAMON AND ITS BIO-ACTIVE COMPONENTS

CONCLUSION: While researchers have explored the multiple spectra of neuroprotective potential of cinnamon and its bioactives in the past decade in numerous preclinical models, only a few clinical studies have been attempted. Nevertheless, few preliminary trials have highlighted the potential cognitive benefits in mild cognitive impairment (MCI) and metabolic disorders linked to neurodegeneration. Further, clinical trials are necessary to establish cinnamon's efficacy, optimal dosage, and safety following long-term intake in neurodegenerative diseases. Developing advanced drug delivery systems, such as nanoformulations and lipid-based carriers, can enhance their bioavailability and brain-targeting potential. In addition, exploring synergistic effects with existing neuroprotective agents may improve therapeutic outcomes. Investigating cinnamon's role in the gut-brain axis and its influence on neuroinflammation could provide deeper insights. Further studies on its molecular mechanisms, including autophagy and mitochondrial function regulation, may help to establish cinnamon as a viable neuroprotective strategy.

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REFERENCES:

1. Sangal A: Role of cinnamon as beneficial antidiabetic food adjunct: a review. Advances in Applied Science Research 2011; 2: 440–450.
2. Vangalapati M, Sree Satya N, Surya Prakash D and Avanigadda S: A review on pharmacological activities and clinical effects of cinnamon species. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2012; 3: 653–663.
3. Charles DJ: Antioxidant properties of spices, herbs and other sources. Springer New York 2013; 145-50.
4. Elshafie MM, Nawar IA, Muhammad A. Algamal MA and Ahmad SM: Evaluation of the biological effects for adding cinnamon volatile oil and TBHQ as an antioxidant on rats lipid profiles. Asian Journal of Plant Sciences 2012; 11: 100-8.
5. Cardoso-Ugarte GA, López-Malo A, Sosa-Morales ME: Cinnamon (*Cinnamomum zeylanicum*) essential oils. In: Essential Oils in Food Preservation, Flavor and Safety. ed: Elsevier 2016; 339-47.
6. Huang TC, Fu HY, Ho CT, Tan D, Huang YT and Pan MH: Induction of apoptosis by cinnamaldehyde from indigenous cinnamon *Cinnamomum osmophloeum* Kaneh through reactive oxygen species production, glutathione depletion, and caspase activation in human leukemia K562 cells. Food Chemistry 2007; 103: 434-43.
7. Rao PV, Gan and SH: Cinnamon: a multifaceted medicinal plant. Evidence Based Compl and Alte Med 2014; 642942.
8. Nakhaee S, Kooshki A, Hormozi A, Akbari A, Mehrpour O and Farrokhfall K: Cinnamon and cognitive function: a systematic review of preclinical and clinical studies. Nutritional Neuroscience 2024; 27: 132–46.
9. Khasnavis S and Pahan K: Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective parkinson disease protein DJ-1 in astrocytes and neurons. Journal of Neuroimmune Pharmacology 2012; 7: 424-35.
10. Lin CH, Chen PK, Wang SH and Lane HY: Effect of sodium benzoate on cognitive function among patients with behavioral and psychological symptoms of dementia: secondary analysis of a randomized clinical trial. JAMA Network Open 2021; 4: 216156.
11. Modi KK, Rangasamy SB, Dasarathi S, Roy A and Pahan K: Cinnamon converts poor learning mice to good learners: implications for memory improvement. Journal of Neuroimmune Pharmacology 2016; 11: 693-707.
12. Senanayake UM, Lee TH and Wills RB: Volatile constituents of cinnamon (*Cinnamomum zeylanicum*) oils. Journal of Agricultural and Food Chemistry 1978; 26: 822-4.
13. Gotmare S and Tambe E: Identification of chemical constituents of cinnamon bark oil by GC-MS and comparative study garnered from five different countries. International Journal of Scientific Research 2019; 19: 35-42.
14. Błaszczyk N, Rosiak A and Kałużna-Czaplińska J: The Potential Role of Cinnamon in Human Health. Forests: An Open Access Journal from MDPI 2021; 12: 648.
15. Adarsh A, Chettiyar B, Kanthesh BM and Raghu N: Phytochemical Screening and Antimicrobial Activity of *Cinnamon zeylanicum*. International Journal of Pharmaceutical Research and Innovation 2020; 13: 22–33.
16. Chen G, Sun F, Wang S, Wang W, Dong J and Gao F: Enhanced extraction of essential oil from *Cinnamomum cassia* bark by ultrasound assisted hydrodistillation. Chinese Journal of Chemistry 2021; 36: 38-46.
17. Tang PL, Chen YT, Qin J, Hou X and Deng J: Effect of cinnamon bark and twig extracts on the chemical, physicochemical and antioxidant properties of fermented milk. Journal of Food Measurement and Characterization 2020; 14: 2271-81.
18. Silva FL, Silva RVS, Branco PC, Costa-Lotufo LV, Murakami C and Young MCM: Chemical composition of the Brazilian native *Cinnamomum stenophyllum* (Meisn.) Vattimo-Gil essential oil by GC-qMS and GCxGC-TOFMS, and its cytotoxic activity. Arabian Journal of Chemistry 2020; 13: 4926–35.
19. Rajini PS: Indian spices and their bio-actives in neurological disorders: In Ayurvedic herbal preparations in Neurological disorders (Eds): M Muralidhara and PS Rajini Academic press. 2023; 541-575; ISBN: 978-0-443019084-1.
20. Gulcin I, Kaya R, Goren AC, Akincioglu H, Topal M and Bingol Z: Anticholinergic, antidiabetic and antioxidant activities of cinnamon (*Cinnamomum verum*) bark extracts: polyphenol contents analysis by LC-MS/MS. International Journal of Food Properties 2019; 22: 1511–26.
21. Shan B, Cai YZ, Sun M and Corke H: Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. Journal of Agricultural and Food Chemistry 2005; 53: 7749-59.
22. Okawa M, Kinjo J, Nohara T and Ono M: DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity of

flavonoids obtained from some medicinal plants. Biological and Pharmaceutical Bulletin 2001; 24: 1202–5.
23. Dhuley N: Anti-oxidant effects of cinnamon (*Cinnamomum verum*) bark and greater cardamon (*Amomum subulatum*) seeds in rats fed high fat diet. Indian Journal of Experimental Biology 1999; 37: 238–42.
24. Kim SJ, Han D, Moon KD and Rhee JS: Measurement of superoxide dismutase-like activity of natural antioxidants. Bioscience, Biotechnology, and Biochemistry 1995; 59: 822–6.
25. Lin CC, Wu SJ, Chang CH and Ng LT: Antioxidant activity of *Cinnamomum cassia*. Phytotherapy Research 2003; 17: 726-30.
26. Beniaich G, Zouirech O, Allali A, Bouslamti M, Maliki I and Moussaoui A: Chemical characterization, antioxidant, insecticidal and anti-cholinesterase activity of essential oils extracted from *Cinnamomum verum* L. Separations 2023; 10: 348.
27. Syarafina ZY, Safithri M, Bintang M and Kurniasih R: *In-silico* screening of cinnamon (*Cinnamomum burmannii*) bioactive compounds as acetylcholinesterase inhibitors. Journal Kimia Sainsdan Aplikasi 2022; 25: 97-107.
28. Saeedi M, Iraji A, Vahedi-Mazdabadi Y, Alizadeh A, Edraki N and Firuzi O: *Cinnamomum verum* J. Presl. Bark essential oil: *in vitro* investigation of anti-cholinesterase, anti-BACE1, and neuroprotective activity.BMC Complementary Medicine and Therapies 2022; 22: 303.
29. Ho SC, Chang KS and Chang PW: Inhibition of neuroinflammation by cinnamon and its main components. Food Chemistry 2013; 138: 2275-82.
30. Fu Y, Yang P, Zhao Y, Zhang L, Zhang Z and Dong X: *trans*-Cinnamaldehyde inhibits microglial activation and improves neuronal survival against neuroinflammation in BV2 microglial cells with lipopolysaccharide stimulation. Evidence- Based Complementary and Alternative Medicine 2017; 4730878.
31. Hwang H, Jeon H and Ock J: 2'-Hydroxycinnamaldehyde targets low-density lipoprotein receptor-related protein-1 to inhibit lipopolysaccharide-induced microglial activation. Journal of Neuroimmunology 2011; 230: 52-64.
32. Chen YFF, Wang YWW, Huang WSS, Lee MMM, Wood WG and Leung YMM: Trans-cinnamaldehyde, an essential oil in Cinnamon powder, ameliorates cerebral ischemia-induced brain injury *via* inhibition of neuroinflammation through attenuation of inos, COX-2 expression and NFκ-B signaling pathway. Neuro Molecular Medicine 2016; 18: 322–33.
33. Bae WY, Choi JS and Jeong JW: The neuroprotective effects of cinnamic aldehyde in an MPTP mouse model of Parkinson's disease. Inter J of Mol Sciences 2018; 19: 551.
34. Mondal S and Pahan K: Cinnamon ameliorates experimental allergic encephalomyelitis in mice *via* regulatory T cells: implications for multiple sclerosis therapy. PLOS ONE 2015; 10: 0116566.
35. Modi KK, Roy A, Brahmachari S, Rangasamy SB and Pahan K: Cinnamon and its metabolite sodium benzoate attenuate the activation of p21rac and protect memory and learning in an animal model of Alzheimer's disease. PLOS ONE 2015; 10: 0130398.
36. Zhang L, Zhang Z, Fu Y, Yang P, Qin Z and Chen Y: Trans-cinnamaldehyde improves memory impairment by blocking microglial activation through the destabilization of iNOS mRNA in mice challenged with lipopolysaccharide. Neuropharmacology 2016; 110: 503-18.
37. Davaatseren M, Jo YJ, Hong GP, Hur HJ, Park S and Choi MJ: Studies on the anti-oxidative function of trans-cinnamaldehyde-included β–cyclodextrin complex. Molecules: a Journal of Synthetic Chemistry and Natural Product Chemistry 2017; 22: 1868.
38. Zhao Y, Deng H, Li K, Wang L, Wu Y and Dong X: Trans-cinnamaldehyde improves neuroinflammation-mediated NMDA receptor dysfunction and memory deficits through blocking NF-κB pathway in presenilin1/2 conditional double knockout mice. Brain, Behavior and Immunity 2019; 82: 45-62.
39. Bektaşoğlu PK, Koyuncuoğlu T, Demir D, Sucu G, Akakın D and Eyüboğlu İP: Neuroprotective effect of cinnamaldehyde on secondary brain injury after traumatic brain injury in a rat model. World Neurosurgery 2021; 153: 392-402.
40. Yulug B, Kilic E, Altunay S, Ersavas C, Orhan C and Dalay A: Cinnamon polyphenol extract exerts neuroprotective activity in Traumatic Brain Injury in male mice. CNS & Neurological Disorders - Drug Targets 2018; 17: 439-447.
41. Pagliari S, Forcella M, Lonati E, Sacco G, Romaniello F and Rovellini P: Antioxidant and anti-inflammatory effect of Cinnamon (*Cinnamomum verum* J. Presl) bark extract after *in-vitro* digestion simulation. Foods 2023; 18: 452.
42. Jana A, Modi KK, Roy A, Anderson JA, van Breemen, RB and Pahan K: Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate: therapeutic implications for neurodegenerative disorders. Journal of Neuroimmune Pharmacology 2013; 8: 739–55.
43. Fadaei S, Asle-Rousta and Masoumeh: Anxiolytic and antidepressant effects of cinnamon (*Cinnamomumverum*) extract in rats receiving lead acetate. Scientific Journal of Kurdistan University of Medical Sciences 2018; 22: 31-9.
44. Nguyen LTH, Nguyen NPK, Tran KN, Shin HM and Yang IJ: Anxiolytic-like effect of inhaled Cinnamon essential oil and its main component cinnamaldehyde in animal models. Molecules 2022; 27: 7997.
45. Zada W, Zeeshan S, Bhatti HA, Mahmood W, Rauf K and Abbas G: *Cinnamomum cassia*: an implication of serotonin reuptake inhibition in animal models of depression. Natural Product Research 2016; 30: 1212-4.
46. Yusha'u Y, Aminu Hanafi A, Muhammad Adam and U: Antidepressant-Like effects of *Cinnamomum verum* on open-space forced swim-induced depression in mice. Nigerian Journal of Physiological Sciences 2023; 38: 223–7.
47. Sohrabi R, Pazgoohan N, Seresht HR and Amin B: Repeated systemic administration of the cinnamon essential oil possesses anti-anxiety and anti-depressant activities in mice. Iranian Journal of Basic Medical Sciences 2017; 20: 708-14.
48. Parisa N, Hidayat, R, Maritska, Z and Prananjaya BA: Antidepressant effect of Cinnamon (*Cinnamomum burmannii*) bark extract in chronic stress-induced rats. Open Access Macedonian Journal of Medical Sciences 2020; 8: 273-7.
49. Aryanezhad M, Abdi M, Amini S, Hassanzadeh K, Valadbeigi E and Rahimi K: *Cinnamomum zeylanicum* extract has antidepressant-like effects by increasing brain-derived neurotrophic factor (BDNF) and its receptor in prefrontal cortex of rats. Avicenna Journal of Phytomedicine 2021; 11: 302–313.
50. Gao ZY, Chen TY, Yu TT, Zhang LP, Zhao SJ and Gu XY: Cinnamaldehyde prevents intergenerational effect of paternal depression in mice *via* regulating GR/miR-190b/BDNF pathway. Acta Pharmacologica Sinica 2022; 43: 1955–69.

51. Ma T, Tang B, Wang Y, Shen M, Ping Y, Wang L and Su J: Cinnamon oil solid self-microemulsion mediates chronic mild stress-induced depression in mice by modulating monoamine neurotransmitters, corticosterone, inflammation cytokines, and intestinal flora. Heliyon 2023; 9: 17125.
52. Kang YJ, Seo DG and Park SY: Phenylpropanoids from cinnamon bark reduced β-amyloid production by the inhibition of β-secretase in Chinese hamster ovarian cells stably expressing amyloid precursor protein. Nutrition Research 2016; 36: 1277-84.
53. Bai L, Li X, Chang Q, Wu R, Zhang J and Yang X: Cinnamaldehyde promotes mitochondrial function and reduces Aβ toxicity in neural cells. Journal of Chinese Pharmaceutical Sciences 2016; 25: 605.
54. Emamghoreishi M, Farrokhi MR, Amiri A and Keshavarz M: The neuroprotective mechanism of cinnamaldehyde against amyloid-β in neuronal SHSY5Y cell line: the role of N-methyl-D-aspartate, ryanodine, and adenosine receptors and glycogen synthase kinase-3β. Avicenna Journal of Phytomedicine 2019; 9: 271-80.
55. Rangasamy SB, Raha S, Dasarathy S and Pahan K: Sodium benzoate, a metabolite of cinnamon and a food additive, improves cognitive functions in mice after controlled cortical impact injury. International Journal of Molecular Sciences 2021; 23: 192.
56. Qubty D, Rubovitch V, Benromano T, Ovadia M and Pick CG: Orally administered Cinnamon extract attenuates cognitive and neuronal deficits following Traumatic Brain Injury.Journal of Molecular Neuroscience 2021; 71: 178–86.
57. Pham HM, Xu A, Schriner SE, Sevrioukov EA and Jafari M: Cinnamaldehyde improves lifespan and healthspan in *Drosophila melanogaster* models for Alzheimer's disease. BioMed Research International 2018; 2018: 3570830.
58. Shaltiel-Karyo R, Davidi D, Frenkel-Pinter M, Ovadia M, Segal D and Gazit E: Differential inhibition of α-synucleinoligomeric and fibrillar assembly in parkinson's disease model by cinnamon extract. Biochimica et Biophysica Acta 2012; 1820: 1628–35.
59. Rao SV, Muralidhara GM and Rajini PS: Neuromodulatory potential of aqueous extracts of cumin, cinnamon: evidence from rotenone model in drosophila: implications to Parkinson's disease. International Journal of Neurology Research 2016; 2: 297-307.
60. Stavinoha R, Gomada Y, Jamison B and Vattem D: *In-vivo* neuroprotective effects of Cinnamon bioactive compounds in *C. elegans* and *D. melanogaster*. Experimental Biology Meeting Abstracts 2015; 29: 1.
61. Guo Y, Zhang Q, Zhang B, Pan T, Ronan EA and Huffman A: Dietary cinnamon promotes longevity and extends health span *via* mTORC1 and autophagy signaling. Aging Cell 2025; 24: 14448.
62. Frydman-Marom A, Levin A, Farfara D, Benromano T, Scherzer-Attali R and Peled S: Orally administrated cinnamon extract reduces β-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models. PLOS ONE 2011; 6: 16564.
63. Peterson DW, George RC and Scaramozzino F: Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease *in-vitro*. Journal of Alzheimer's Disease 2009; 17: 585-97.
64. Do J, Kim N, Jeon SH, Gee MS, Ju YJ and Kim JH: Trans-cinnamaldehyde alleviates amyloid-beta pathogenesis via the SIRT1-PGC1α-PPARγ pathway in 5XFAD transgenic mice. International Journal of Molecular Sciences 2020; 21: 4492.
65. Mustafa HN: Neuro-amelioration of cinnamaldehyde in aluminum-induced Alzheimer's disease rat model. Journal of Histotechnology 2020; 43: 11-20.
66. Lin J, Song Z, Chen X, Zhao R, Chen J, Chen H and Wu Z: Trans-cinnamaldehyde shows anti-depression effect in the forced swimming test and possible involvement of the endocannabinoid system. Biochemical and Biophysical Research Communications 2019; 518: 351-6.
67. Saeed M, Ghadiri A, Hadizadeh F, Attaranzadeh A, Alavi MS and Etemad L: Cinnamaldehyde improves methamphetamine-induced spatial learning and memory deficits and restores ERK signaling in the rat prefrontal cortex. Iranian Journal of Basic Medical Sciences 2018; 21: 1316-1321.
68. Jahromi Z, Mohammadghasemi F, Moharrami Kasmaie F and Zaminy A: Cinnamaldehydeenhanced functional recovery after sciatic nerve crush injury in rats. Cells Tissues Organs 2020; 209: 43-53.
69. Soukhaklari R, Borhani-Haghighi A, Farsadrooh A, Moezi L, Pirsalami F and Kazerouni A: The effect of cinnamaldehyde on passive avoidance memory and hippocampal Akt, ERK and GSK-3β in mice. European Journal of Pharmacology 2019; 859: 172530.
70. Abou El-ezz D, Maher A, Sallam N, El-Brairy A and Kenawy S: Trans-cinnamaldehyde modulates hippocampal Nrf2 factor and inhibits amyloid beta aggregation in LPS-induced neuroinflammation mouse model. Neurochemical Research 2018; 43: 2333-42.
71. Golmakani MR, Abrari K, Goudarzi I, Khodaparast A and Bagheri F: Protective role of eugenol against the destructive effects of lead on conditioned fear memory in male rats with post-traumatic stress disorder-related behavioral traits. IBRO Neuroscience Reports 2024; 16: 395-402.
72. Taheri P, Yaghmaei P, Tehrani HS and Ebrahim-Habibi A: Effects of eugenol on Alzheimer's disease-like manifestations in insulin-and Aβ-induced rat models. Journal of Neurophysiology 2019; 51: 114-9.
73. Akbar L, Juliandi B, Boediono A, Batubara I and Subangkit M: Effects of Eugenol on Memory Performance, Neurogenesis, and Dendritic Complexity of Neurons in Mice Analyzed by Behavioral Tests and Golgi Staining of Brain Tissue. Journal of Stem Cells and Regenerative Medicine 2021; 26: 35-41.
74. Chandra S, Roy A, Jana M and Pahan K: Cinnamic acid activates PPARα to stimulate Lysosomal biogenesis and lower Amyloid plaque pathology in an Alzheimer's disease mouse model. Neurobiology of Disease 2019; 124: 379-95.
75. Salehi O, Sheikholeslami-Vatani D, Negarandeh Z and Yarahmadi J: The effect of swimming training at different temperatures with Cinnamon consumption on avoidance memory, spatial memory and aerobic power in Streptozotocin-induced diabetic rats. Research in Sports, Science, Medicine and Plants 2020; 1: 67-8.
76. Roghani M, Mehraein F, Zamani M, Negahdar F and Shojaee A: The effects of aqueous cinnamon bark extract and cinnamaldehyde on neurons of *Substantia nigra* and behavioral impairment in a mouse model of Parkinson's disease. Journal of Basic and Clinical Pathophysiology 2017; 5: 27-32.
77. Madhavadas S and Subramanian S: Cognition enhancing effect of the aqueous extract of *Cinnamomum zeylanicum* on non-transgenic Alzheimer's disease rat model: Biochemical, histological, and behavioural studies. Nutritional Neuroscience 2016; 20: 526–37.

78. Tuloeghamary M, Ahmadi R and Pishghadam S: Effect of intraperitoneal injection of Cinnamon (*Cinnamonum zeylanicum*) hydroalcoholic extract on passive avoidance learning in male rats with streptozotocin-induced model of Alzheimer's disease. Daneshvar Medicine: Basic and Clinical Research Journal 2017; 24: 1-7.
79. Sayad-Fathi S, Zaminy A, Babaei P, Yousefbeyk F, Azizi N and Nasiri E: The methanolic extract of *Cinnamomum zeylanicum* bark improves formaldehyde-induced neurotoxicity through reduction of phospho-tau (Thr231), inflammation, and apoptosis. EXCLI Journal: Experimental and Clinical Sciences 2020; 19: 671-686.
80. Raha S, Dutta D, Roy A and Pahan K: Reduction of Lewy body pathology by oral cinnamon. Journal of Neuroimmune Pharmacology 2021; 16: 592-608.
81. Maalouly G, Martin C-M-A, Baz Y, Saliba Y, Baramili A-M and Fares N: Antioxidant and anti-apoptotic neuroprotective effects of cinnamon in imiquimod-induced lupus. Antioxidants 2024; 13: 880.
82. Kalia V, Devgan N, Mani S: Effect of cinnamon and honey on on-time and off-time in Parkinson's disease: A case report. J of the Gujarat Res Socie 2019; 21: 650-654.
83. Zareie A, Sahebkar A, Khorvash F, Bagherniya M, Hasanzadeh A and Askari G: Effect of cinnamon on migraine attacks and inflammatory markers: A randomized double-blind placebo-controlled trial. Phytotherapy Research 2020; 34: 2945-52.
84. Han HS, Koo SY and Choi KY: Emerging nanoformulation strategies for phytocompounds and applications from drug delivery to phototherapy to imaging. Bioactive Materials 2022; 14: 182-205.
85. Fachriyah E, Eviana I, Eldian O, Amaliyah N and Sektianingrum A: Antidiabetic activity from gallic acid encapsulated nanochitosan. In*:* Proceedings of the 11th joint conference on chemistry in conjunction with the 4th regional biomaterials scientific meeting, Purwokerto, Indonesia 2017; 172: 012042.
86. Culas MS, Popovich DG and Rashidinejad A: Recent advances in encapsulation techniques for cinnamon bioactive compounds: A review on stability, effectiveness, and potential applications. Food Bioscience 2024; 57: 103470.
87. Lv C, Yuan X, Zeng HW, Liu RH and Zhang WD: Protective effect of cinnamaldehyde against glutamate-induced oxidative stress and apoptosis in PC12 cells. European Journal of Pharmacology 2017; 815: 487-94.
88. Maiolo SA, Fan P and Bobrovskaya L: Bioactive constituents from cinnamon, hemp seed and polygonumcuspidatum protect against H_2O_2 but not rotenone toxicity in a cellular model of Parkinson's disease. Journal of Traditional and Complementary Medicine 2018; 8: 420-7.
89. Schink A, Naumoska K, Kitanovski Z, Kampf CJ, Fröhlich-Nowoisky J and Thines E: Anti-inflammatory effects of cinnamon extract and identification of active compounds influencing the TLR2 and TLR4 signaling pathways. Food & Function 2018; 11: 5950-64.
90. Adefegha SA, Okeke BM & Oboh G: Antioxidant properties of eugenol, butylated hydroxylanisole, and butylated hydroxyl toluene with key biomolecules relevant to Alzheimer's diseases *in-vitro*. Journal of Food Biochemistry 2021; 45: 13276.
91. Ramazani E, Yazd Fazeli M, Emami, SA, Mohtashami L, Javadi B and Asili J: Protective effects of *Cinnamomum verum*, *Cinnamomum cassia* and cinnamaldehyde against 6-OHDA-induced apoptosis in PC12 cells. Molecular Biology Reports 2020; 47: 2437-45.
92. Nawaz A, Ali T, Naeem M, Hussain F, Li Z and Nasir A: Biochemical, structural characterization and *in-vitro* evaluation of antioxidant, antibacterial, cytotoxic, and antidiabetic activities of nanosuspensions of *Cinnamomum zeylanicum* bark extract. Frontiers in Chemistry 2023; 11: 1194389.

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