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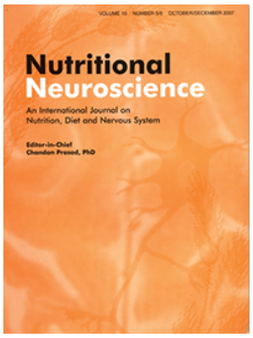

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Cinnamon and cognitive function: a systematic review of preclinical and clinical studies

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ABSTRACT

Cinnamon is the inner bark of trees named Cinnamomum. Studies have shown that cinnamon and its bioactive compounds can influence brain function and affect behavioral characteristics. This study aimed to systematically review studies about the relationship between cinnamon and its key components in memory and learning. Two thousand six hundred five studies were collected from different databases (PubMed, Scopus, Google Scholar, and Web of Science) in September 2021 and went under investigation for eligibility. As a result, 40 studies met our criteria and were included in this systematic review. Among the included studies, 33 were *In vivo* studies, five were *In vitro*, and two clinical studies were also accomplished. The main outcome of most studies (n = 40) proved that cinnamon significantly improves cognitive function (memory and learning). In vivo studies showed that using cinnamon or its components, such as eugenol, cinnamaldehyde, and cinnamic acid, could positively alter cognitive function. In vitro studies also showed that adding cinnamon or cinnamaldehyde to a cell medium can reduce tau aggregation, Amyloid β and increase cell viability. For clinical studies, one study showed positive effects, and another reported no changes in cognitive function. Most studies reported that cinnamon might be useful for preventing and reducing cognitive function impairment. It can be used as an adjuvant in the treatment of related diseases. However, more studies need to be done on this subject.

KEYWORDS

Cinnamon; memory; learning; cognitive function; Alzheimer's disease

1. Introduction

Various neurodegenerative and non-neurodegenerative diseases may cause memory and cognitive impairments. As much as memory plays an important role in learning, such diseases can affect it [1,2]. For example, Alzheimer's is a neurodegenerative disease accompanied by memory deficits and other symptoms such as confusion and disorientation [3].

Amyloid-β plaque and tau neurofibrillary tangles have a remarkable role in triggering neurodegeneration in Alzheimer's disease [4]. Some evidence shows that overproduction of amyloid-β can lead to impaired memory, oxidative damage, and cognitive impairment [5,6]. So far, various plant species and plant-derived bioactive phytochemicals have been introduced with potential neuroprotective roles that can improve Alzheimer's disease and brain functions [7]. Cinnamon (*Cinnamomum Verum*) is a spice with a long history in different cultures. It is known as a common herbal medicine that has been used for centuries. It has been considered safe according to the United States Food and Drug Administration (USFDA) and categorized as GRAS (generally recognized as safe) [8].

Cinnamomum has two main subcategories: *Cinnamomum zeylanicum*, commonly known as true Cinnamon or Ceylon cinnamon, and *Cinnamon cassia*, better known as Chinese cinnamon/*Cinnamomum aromaticum* [9]. *Cinnamomum zeylanicum* has been reported to have a richer source of antioxidants and bioactive compounds than *Cinnamon cassia* [10]. Cinnamaldehyde, eugenol, and trans-cinnamaldehyde are the principal components of cinnamon [7,11]. Catechin, tannin, syringic acid, and epigallocatechin gallate are the major phenolic compounds of cinnamon. While cinnamaldehyde, eugenol, and cinnamic acid are its major volatile oils [7,12,13].

Cinnamon possesses anti-inflammatory, antioxidant, anticancer, cognitive function, and immunomodulatory properties, according to *In vitro* and *In vivo* studies [1,2]. Cinnamon is proven to have antioxidant properties and reduce inflammation through different pathways, such as the NF-kB pathway and reducing

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reactive oxygen species (ROS) [14]. Eugenol, cinnamic acid, cinnamaldehyde, syringic acid, and Catechin have antiproliferative, anti-inflammatory, and antioxidant effects [7,13,15]. Also, the components of cinnamon have potential neuroprotective effects. Also, they can play a preventive and adjuvant role in Alzheimer's disease pathogenesis [16]. Cinnamaldehyde inhibits Amyloid-Beta aggregation and increases cell survival by reducing IL-1 ß and caspase-3 [17]. Also, cinnamaldehyde can be beneficial in brain disorders associated with aging due to its influence on the NO system [18]. Cinnamic acid and eugenol are indicated to prevent Amyloid-Beta accumulation in different tissues, including the brain [19,20]. Choline also is known to be a bioactive component in cinnamon species. It is essential in producing acetylcholine, a well-known neurotransmitter that plays a role in cognitive function [21]. Therefore, it might benefit cognitive function (memory and learning) impairment [22]. To our knowledge, no study systematically evaluated the effects of this compound on cognitive function. Therefore, due to the lack of systematic review in this field, we aimed to conduct a systematic review on the effect of cinnamon and its components on cognitive function (memory and learning) in humans and other species and cell lines.

2. Methods

2.1. Design and search strategy

This systematic review has been written under PRISMA guidelines. Moreover, the ARRIVE guideline was applied to experimental studies. The completed PRISMA checklist and a checklist for animal studies [23] were provided as supplementary files. Two independent researchers conducted a comprehensive search until Sept 14, 2021, using combinations of keywords and MESH terms in the title or abstract of studies in different databases/search engines: Web of Science, Google scholar, PubMed, and Scopus. The search strategies used in different databases have been reported in Table 1. The search process was managed using Endnote software.

2.2. Eligibility criteria and study selection

2.2.1. Inclusion criteria

Studies that assessed the effects of cinnamon or its components on cognitive function (memory and learning) in humans or animals using behavioral tests were included. Also, *In vitro* studies that measured amyloid-β plaque, tau aggregation, and neural survival in cell lines were considered.

In this study, age, gender, species, exposure, sample size, and duration of intervention were not restricted. In addition, we included papers published in English or with an English abstract that was sufficiently descriptive. The reference lists of the identified papers were also reviewed to seek more relevant articles.

2.2.2. Exclusion criteria

The review articles, letters, conference proceedings, and books were not included. In addition, because the underlying mechanisms presented in different studies are not definitive, we did not include *in vivo* and clinical studies assessing cinnamon effects' underlying mechanisms in this systematic review.

In addition, the total results of databases were obtained and pooled together, and duplicate studies were removed using Mendeley. The remaining articles were scanned by 'title' and 'abstract.' Irrelevant articles were excluded from our excel file, the remaining studies were under investigation by their full text, and those that did not meet inclusion criteria were excluded. Finally, all the screening processes were double-checked by three independent individuals.

2.3. Data extraction

The data fields were extracted and are shown in Table 2. The following information was obtained from each study: first author, year of publication, target component, study population (or groups), sample size (or numbers of each group), dosages of cinnamon or concentration of the component of interest, gender, animal model, age (for human studies), route of administration, cell line (for in vitro studies), model of cognitive/memory deficit (for in vivo studies), duration of consumption (for human and in vivo studies), a proposed mechanism (for in vivo studies), outcome and results. Three independent reviewers extracted the needed data.

2.4. Quality assessment

Predefined checklists were used to control the eligibility of studies. Two reviewers independently evaluated each study using the Joanna Briggs Institute's (JBI) Critical Appraisal of Evidence Effectiveness tool for clinical and *In vitro* studies. This JBI tool contains components requiring a two-way yes / no answer, with a yes answer one score and a no / unclear answer a zero point [24]. The ARRIVE 2.0 Essential 10 guideline for reporting in vivo experiments in animal

Table 1. Search Strategies in different databases for retrieving the relevant documents.

Database/ search engine	Search strategy	Results
Pub Med	((((((((((((Cinnamon [MeSH Terms]) OR cinnamaldehyde ([MeSH Terms])) OR cinnamate ([Supplementary Concept])) OR (cinnamic acid [Supplementary Concept])) OR (methyl cinnamate [Supplementary Concept])) OR (ethyl cinnamate [Supplementary Concept])) OR (Eugenol[MeSH Terms]))) OR (cinnamyl acetate [Supplementary Concept])) OR (coumarin [Supplementary Concept])) OR (Cinnamomum zeylanicum[MeSH Terms])) OR (Cinnamomum aromaticum[MeSH Terms])) OR (Cinnamomum verum[MeSH Terms])) AND ((((((((((((memory[MeSH Terms]) OR (learning[MeSH Terms])) OR (dementia [MeSH Terms])) OR (amnesia[MeSH Terms])) OR (Alzheimer Disease[MeSH Terms])) OR (cognition [MeSH Terms])) OR (Cognitive Dysfunction[MeSH Terms])) OR (Mental Recall[MeSH Terms])) OR (Hippocampus[MeSH Terms])) OR (Amyloid beta-Peptides[MeSH Terms])) OR (tau Proteins[MeSH Terms])) OR (Cognition Disorders[MeSH Terms])) OR (Neurocognitive Disorders[MeSH Terms]))	643
	((((((((((((((((((((((((cinnamon [Title/Abstract]) OR cinnamaldehyde ([Title/Abstract])) OR (cinnamate [Title/Abstract])) OR (cinnamic acid [Title/Abstract])) OR (methyl cinnamate [Title/Abstract])) OR (ethyl cinnamate [Title/Abstract])) OR (Eugenol [Title/Abstract])) OR (cinnamyl acetate [Title/Abstract])) OR (coumarin [Title/Abstract])) OR (Cinnamomum zeylanicum [Title/Abstract])) OR (Cinnamomum aromaticum[Title/Abstract])) OR (Cinnamomum verum[Title/Abstract])) OR (cassia cinnamon[Title/Abstract])) OR (cinnamon cassia[Title/Abstract])) OR (cinnamon ceylon[Title/Abstract])) OR (ceylon cinnamon[Title/Abstract]))) OR (Chinese cinnamon[Title/Abstract])) OR (ceylon Cinnamomum[Title/Abstract])) OR (Cinnamomum ceylon[Title/Abstract])) OR (cassia Cinnamomum[Title/Abstract])) OR (Cinnamomum cassia[Title/Abstract])) OR (Cinnamomum[Title/Abstract])) AND ((((((((((((((((((((((memory[Title/Abstract]) OR (learning[Title/Abstract])) OR (dementia[Title/Abstract])) OR (amnesia[Title/Abstract])) OR (Alzheimer Disease[Title/Abstract])) OR (cognition[Title/Abstract])) OR (Cognitive Dysfunction[Title/Abstract])) OR (Mental Recall[Title/Abstract])) OR (Hippocampus[Title/Abstract])) OR (Amyloid beta-Peptides[Title/Abstract])) OR (tau Proteins[Title/Abstract])) OR (Cognition Disorders[Title/Abstract])) OR (Neurocognitive Disorders[Title/Abstract])) OR (Alzheimer Diseases[Title/Abstract])) OR (memorizing[Title/Abstract])) OR (memorization[Title/Abstract])) OR (awareness[Title/Abstract])) OR (consciousness[Title/Abstract])) OR (cognitive[Title/Abstract])) OR (Alzheimer ABP[Title/Abstract])) OR (alzheimer's disease[Title/Abstract])) OR (alzheimer's diseases[Title/Abstract]))	447
Scopus	TITLE-ABS ((memory OR learning OR dementia OR amnesia OR 'Alzheimer Disease' OR cognition OR 'cognitive dysfunction' OR 'mental recall' OR hippocampus OR 'Amyloid-beta' OR 'tau Protein' OR 'Cognition Disorders' OR cognitive OR 'Neurocognitive Disorders' OR 'Alzheimer Diseases' OR memorizing OR memorization OR consciousness OR 'Alzheimer's disease' OR 'Alzheimer's diseases' OR Alzheimer) AND (cinnamate OR cinnamon OR cinnamaldehyde OR 'cinnamic acid' OR 'methyl cinnamate' OR 'ethyl cinnamate' OR eugenol OR 'cinnamyl acetate' OR coumarin OR 'Cinnamomum zeylanicum' OR 'Cinnamomum aromaticum' OR 'Cinnamomum verum' OR Cinnamomum OR 'Cinnamomum cassia' OR 'cassia Cinnamomum' OR 'Cinnamomum Ceylon' OR 'Ceylon Cinnamomum' OR 'Chinese cinnamon' OR 'Ceylon cinnamon' OR 'cinnamon Ceylon' OR 'cinnamon cassia' OR 'cassia cinnamon)')	683
Web of Science	ab = ((memory OR learning OR dementia OR amnesia OR 'Alzheimer Disease' OR cognition OR 'cognitive dysfunction' OR 'mental recall' OR hippocampus OR 'Amyloid-beta' OR 'tau Protein' OR 'Cognition Disorders' OR cognitive OR 'Neurocognitive Disorders' OR 'Alzheimer diseases' OR memorizing OR memorization OR awareness OR consciousness OR 'Alzheimer's disease' OR 'Alzheimer's diseases' OR Alzheimer AND cinnamate OR Cinnamon OR cinnamaldehyde OR 'cinnamic acid' OR 'methyl cinnamate' OR 'ethyl cinnamate' OR eugenol OR 'cinnamyl acetate' OR coumarin OR 'Cinnamomum zeylanicum' OR 'Cinnamomum aromaticum' OR 'Cinnamomum verum' OR Cinnamomum OR 'Cinnamomum cassia' OR 'cassia Cinnamomum' OR 'Cinnamomum Ceylon' OR 'Ceylon Cinnamomum' OR 'Chinese cinnamon' OR 'Ceylon cinnamon' OR 'cinnamon Ceylon' OR 'cinnamon cassia' OR 'cassia cinnamon))"	612
	ti = ((memory OR learning OR dementia OR amnesia OR 'Alzheimer Disease' OR cognition OR 'cognitive dysfunction' OR 'mental recall' OR hippocampus OR 'Amyloid-beta' OR 'tau Protein' OR 'Cognition Disorders' OR cognitive OR 'Neurocognitive Disorders' OR memorizing OR memorization OR awareness OR consciousness OR 'Alzheimer's disease' OR 'Alzheimer's diseases' OR Alzheimer) AND (cinnamate OR cinnamon OR cinnamaldehyde OR 'cinnamic acid' OR 'methyl cinnamate' OR 'ethyl cinnamate' OR eugenol OR 'cinnamyl acetate' OR coumarin OR 'Cinnamomum zeylanicum' OR 'Cinnamomum aromaticum' OR 'Cinnamomum verum' OR Cinnamomum OR 'Cinnamomum cassia' OR 'cassia Cinnamomum' OR 'Cinnamomum Ceylon' OR 'Ceylon Cinnamomum' OR 'Chinese cinnamon' OR 'Ceylon cinnamon' OR 'cinnamon Ceylon' OR 'cinnamon cassia' OR 'cassia cinnamon)')	125
Google Scholar	allintitle:(memory OR learning OR dementia OR Alzheimer OR cognition OR cognitive OR 'Neurocognitive Disorders' OR hippocampus) (Cinnamon OR cinnamaldehyde OR coumarin OR Cinnamomum OR eugenol OR cinnamate)	95

research was used for the quality assessment of experimental studies. ARRIVE 2.0 is used to improve the reporting quality of animal studies, and it includes 21 items and 38 sub-items. Essential 10 includes ten items and 22 sub-items, which are basic items that must be included in animal studies. This includes different aspects of the study, including; 'study design, sample size, inclusion and exclusion criteria, randomization, blinding, measurement result, statistical methods, experimental animals, experimental procedures, and results [25,26]. A third person resolved any inconsistencies. After quality assessment, the studies checked most criteria and were included (70% or above). Therefore, no studies were excluded at this stage due to the lack of quality scores.

3. Results

3.1. Selection of studies

Two thousand six hundred five studies were obtained from different databases, and 803 articles were excluded as duplicates. After screening titles and abstracts, 1551 irrelevant studies were removed, and the 251 remaining studies went under investigation by their full text. Two hundred eleven studies were excluded for reasons

Table 2. Characteristics of included animal studies on the effects of cinnamon/its components on cognitive function (memory and learning).

First author & publication year	Animal model	Gender	Cinnamon/ component	Groups	Number in each group	Dosage of Cinnamon/ component	Normal/Model of cognitive function deficit	Route of administration	Duration of consumption (treatment for impaired models)	Proposed mechanism	Behavioral test	Results
Akbar L 2021 [56]	12 week DDY mice	Male	Eugenol	3 (control, 30 mg/kg, 100 mg/kg)	7	30 mg/kg 100 mg/kg	Normal	Oral	30 days	Positive effect on dendritic complexity in the dentate gyrus and basal area	Y Maze (spatial memory) NOR (recognition memory) MWM (learning memory and spatial memory)	Both dosages had a positive effect on improving spatial memory performance (Y Maze) positive effect on recognition memory (NOR test) but in learning-memory (MWM test) didn't show a significant effect
Zhao Y 2019 [34]	Wistar rats (AlCl3-induced and normal rats)	Both	Eugenol	5 (control, negative control (AlCl3 induced), AlCl3 + Rivastigmine, AlCl3 + eugenol, AlCl3 + eugenol + rivastigmine)	6	50 mg/kg	Aluminum Chloride-induced dementia	Oral	10 days	Decreasing AchE, lipid peroxidation (TBARS), and nitrite level; increase catalase, SOD, and GSH levels	MWM (learning memory and spatial memory)	Eugenol showed a significant reversal of memory deficit dementia on AD type (MWM test showed positive effect)
Ahmadi R 2017 [42]	Wistar rats	Male	Cinnamon extract (hydro-alcoholic)	5 (control injection DMSO i.p, control B with surgery and CSF injection of DMSO, Alzheimer group with surgery and injection of STZ to CSF, experimental group surgery + STZ injection to CSF + i.p Injectioninjection of cinnamon extract)	6	125 mg/kg	Streptozotocin (STZ) injection to CSF	IP	4 days	NM	Shuttle box (learning)	Positive on passive effect learning in AD models (shuttle box)
Salehi O 2020 [43]	Diabetic rates (streptozotocin)	NM	Cinnamon extract (aqueous)	7(healthy control, diabetic control, S5c, S5c + cin, S35c, S35c + cin, cin)	8	200 mg/kg/day	Streptozotocin (STZ)	Oral	8 weeks, 3 days per week	NM	Y Maze (spatial memory)	Overall positive effects on avoidance and spatial memory (Y Maze and avoidance memory)
Hemmati A A 2018 [12]	Mice	Male	Cinnamic acid	6 (normal control, normal + cinnamic acid, diabetic control, diabetic + 10 mg/kg/day cinnamic acid, diabetic + 20 mg/kg/day cinnamic acid, diabetic + 40 mg/kg/day cinnamic acid)	8	20 mg/kg/day (normal mice) 10 mg/kg/day 20 mg/kg/day 40 mg/kg/day (diabetic mice)	Streptozotocin (STZ)	IP	40 days	Inhibition of ROS production and preventing GSH decrease in diabetic mice and decreasing MDA and increasing SOD	MWM (learning memory and spatial memory) Cross-arm maze (navigation memory) Passive avoidance test (learning and memory)	Cinnamic acid improves spatial and passive avoidance memory in the brain of diabetic mice (MWM test, cross-arm Maze, step-down passive avoidance task)
Vahidi A 2012 [44]	Rats	Male	Cinnamon extract (hydro-alcoholic)	4 (control group with saline, 125, 250, and 500 mg/kg groups)	5	125 mg/kg 250 mg/kg 500 mg/kg	Normal	IP	3 days	NM	Shuttle box (learning and short memory)	Decrease in memory, no change in learning, and decrease in learning with increasing the dosage (125 mg/kg showed no change in learning as 250 & 500 mg/kg showed a decrease in learning)
Lui Z 2013 [45]	Sprague Dawley rat	NM	Eugenol	6 (normal control group, AD control group, AD with cut olfactory nerve, Xiu three-needle group, eugenol group, combined acupuncture and eugenol group)	10	Spray on the medical cotton	Amyloid-Beta1-40	Olfactory (smelling)	6 courses (once a day for 5 days and a 2 days interval)	Increase in GSH-Px and SOD and decrease in MDA	MWM (learning memory and spatial memory)	Positive in learning-memory (MWM test)
Taheri P 2019 [15]	Wistar rats	Male	Eugenol	7 (control group, insulin Amyloid (ia) and solvent, ia + 0.01 mg/kg, ia + 0.02 mg/kg, Amyloid-Beta treated rats, Amyloid-Beta + 0.01 mg/kg, Amyloid-Beta + 0.02 mg/kg)	7	0.01 mg/kg 0.02 mg/kg	Insulin Amyloid and Amyloid-Beta	I.P	14 days	Decreasing Amyloid plaque in the hippocampus on 0.01 mg/kg dosage	Step through latency (memory and learning)	All four AD model groups (ia and AB) showed a significant positive result on memory (step-through latency), and the histological study showed a positive effect on

												the reduction of amyloid plaques (both histological and behavioral studies showed more significant change in 0.01 mg/kg dose)
Mustafa HN 2020 [46]	Wistar rats	Male	Aqueous Cinnamon extract (dissolved in water and boiled) (ACE)	4	(control group, 200 mg/kg, ACI3 group, AlC3 + 200 mg/kg cinnamon extract group)	10	200 mg/kg (normal and AlC3 induced)	Aluminum Chloride-induced dementia	Oral	60 days	Reduced amyloid plaque in cerebellar histology, decrease in GFAP+, and increase in Purkinje cells	T Maze (spatial learning and memory)	Positive on memory (T-maze test) and ACE played a protective role against Amyloid-Beta formation.
Ryu JS 2020 [61]	C57b1 mice	Male	Trans-cinnamaldehyde	5	(control group, D-gal + AlC3 group, D-gal + AlC3 + TCA group, D-gal + AlC3 + treadmill, D-gal + AlC3 + TCA + treadmill)	12	30 mg/kg/day	D-galactose and aluminum chloride	IP	35 days	Increase in SOD, Nrf2 and NAD(P)H dehydrogenase	MWM (learning memory and spatial memory) Y Maze (spatial memory)	Positive on cognitive function (positive result on Y-Maze but no significant change in MWM test)
Teymuori M 2021 [58]	Mice	Male	Cinnamon zeylanicum extract (alcoholic)	5	(vehicle group with saline, positive control group rivastigmine, piper nigrum 50 & 100 mg/kg, cinnamon zeylanicum 100, 200 & 400 mg/kg, both PN (50 mg/kg) and CZ (100 and 400 mg/kg))	6	100 mg/kg 200 mg/kg 400 mg/kg	scopolamine (1 mg/kg, ip)	IP	8 days	NM	Passive avoidance test (learning and memory) NOR (recognition memory)	No significant change in the passive avoidance test, but in the object recognition test, 100 mg/kg showed an increase (no change in 200 & 400 mg/kg)
Sayad-Fathi S 2020 [47]	Wistar rats	Male	Cinnamon zeylanicum alcoholic extract (CE)	6	(sham group, accumulation of formaldehyde 60 mg/kg, three experimental groups of 100, 200 & 400 mg/kg of CE after FA treatment, control group receiving cinnamon extract solvent after FA treatment)	7	100 mg/kg 200 mg/kg 400 mg/kg	Formaldehyde	Oral	30 days	Decrease in phospho-tau and apoptotic/intact neuron's ratio	MWM (learning memory and spatial memory) Passive avoidance test (learning and memory)	CE co-treatment in the MWM test with dosages of 100 & 200 mg/kg showed a decrease in escape latency; however, only the 200 mg/kg group showed an increase in the time spent in the target quadrant. But in the passive avoidance task, no group showed a significant change
Jawale A 2016 [48]	Sprague Dawley rats	Male	Cinnamaldehyde	6	(control, diabetic control, normal + cinnamaldehyde 40 mg/kg, diabetic + cinnamaldehyde 10 mg/kg, diabetic + cinnamaldehyde 20 mg/kg, diabetic + cinnamaldehyde 40 mg/kg)	8 8 6 7 7 7	10 mg/kg 20 mg/kg 40 mg/kg	High-fat diet and low dose of streptozotocin (STZ) treatment	Oral	21 days	Reduction in TNF- α and IL-6 levels, decrease in AchE activity	Elevated plus maze (anxiety-like behavior) MWM (learning memory and spatial memory)	Elevated Plus Maze test showed a positive effect for 40 mg/kg (diabetic), but 10 and 20 mg/kg failed to show any significant change in Morris water test. CA did not make a significant change in non-diabetic animals, although it was a significant positive change in 20 & 40 mg/kg in diabetic animals
Raha S 2020 [59]	A53T mice NTG mice	NM	Cinnamon powder and sodium benzoate (NaB) mixed with 0.5% methylcellulose (MC)	3	(NTg mice, A53T, A53T + cinnamon)	5 or 6	100 mg/kg/d (100 µL cinnamon mixed with MC and 100 µL NaB mixed with MC)	Transgenic mice (expressing mutant A53T human a-synucleinopathies)	Oral	60 days	Reducing α-synuclein protein	Barnes test (spatial learning and memory)	Positive effect on cognitive function decrease in a-syn in A53T mice treated with cinnamon in Barnes Maze (spatial learning and memory), the group that treated cinnamon showed significantly less time to reach the goal box
Nikbin S 2020 [49]	Wistar rats	Male	Eugenol	8	(sedentary control, Exercise, Chlorpyrifos, Control + Corn Oil, Control + Dimethylsulfoxide, Chlorpyrifos + Eugenol, Chlorpyrifos + Exercise, Chlorpyrifos + Exercise + Eugenol)	8	250 mg/kg	Hippocampus apoptosis induced by Chlorpyrifos	IP	4 weeks	No effect on AchE and BDNF	Shuttle box (avoidance memory)	Positive on avoidance memory (shuttle box, instruction, memory, and avoidance test)
Anderson RA 2013 [35]	Wistar rats	Male	Cinnamon powder (*Cinnamomum burmannii*)	4	(Control, High Fat/High Fructose, Control +	20	20 g/Kg	High Fat/ A high Fructose Diet induces Behavior, Brain Insulin	oral	12 weeks	decreased in Tau and Aβ precursor protein	Elevated plus maze (anxiety-like behavior)	Positive on cognition (Y-Maze, the elevated plus-maze), cinnamon has protective

(*Continued*)

Table 2. Continued.

First author & publication year	Animal model	Gender	Cinnamon/ component	Groups	Number in each group	Dosage of Cinnamon/ component	Normal/Model of cognitive function deficit	Route of administration	Duration of consumption (treatment for impaired models)	Proposed mechanism	Behavioral test	Results
				Cinnamon, High Fat/High Fructose + Cinnamon)			Signaling And Alzheimer-Associated Changes				Y Maze (spatial learning and memory)	role against formation of Tau, and Amyloid precursor protein
Modi KK 2015 [60]	5XFAD Mice	Male	Cinnamon powder mixed in 0.5% methylcellulose (MC)	5 (Non-Transgenic, 5XFAD-Tg, Tg + Cinnamon, Tg + sodium benzoate Tg + Vehicle)	10	100 mg/kg	Amyloid Beta1-42	oral	20 days (once every two days)	Inhibition of neural apoptosis, glial activation and Aβ accumulation	Barnes test (spatial learning and memory) T Maze (spatial learning and memory) NOR (recognition memory)	Positive on protection of Amyloid Beta formation, improvement of memory (Barnes test, T maze test and NOR)
Chandra S 2019 [20]	5XFAD mice	Both	Trans cinnamic acid	5 (Non Transgenic, 5XTransgenic/Para-/-+Vehicle, 5XTransgenic/ Para-/-+ Cinnamic acid, 5XTransgenicg + Cinnamic acid, 5XTransgenic + Vehicle)	NM	100 mg/kg	Transgenic Mice expressing PPARa	oral	30 days	Decrease Aβ plaque	Barnes test (spatial learning and memory) T Maze (spatial learning and memory)	Positive on reduction of Amyloid Beta plaque and spatial memory improvement (Barnes test and T Maze test)
Soukhaklari R 2019 [50]	Mice	Male	Cinnamaldehyde	8 (Control – Cinnamaldehyde groups at doses 12.5 mg/kg, 25 mg/kg, 30 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg and 100 mg/kg)	7-10	12.5 mg/kg 25 mg/kg 30 mg/kg 40 mg/kg 45 mg/kg 50 mg/kg 100 mg/kg	normal	oral	10 days	Increase phosphorylated Akt, ERK and GSK-3β on 45,50 and 100 mg/kg doses	Passive avoidance test (learning and memory)	Biphasic effect of cinnamaldehyde 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 mg/kg, 25 mg/kg, 30 mg/kg, and 40 mg/kg (passive avoidance memory test)
Malik J 2015 [36]	Wistar rats	Male	Lyophilized Aqueous extract of Cinnamomum zeylanicum	7 (Vehicle, Streptozotocin, donepezil, Lyophilized Cinnamomum Zezlanicum Extract at doses 50 mg/kg, 100 mg/kg, 200 mg/kg, and 200 mg/kg)	8	50 mg/kg 100 mg/kg 200 mg/kg	Streptozotocin-induced dementia	oral	20 days	Reduce AchE, MDA, and GSH dose-dependently	NOR (recognition memory) MWM (learning memory and spatial memory)	improvement of retention and recognition, Spatial memory, and learning (NOR test and MWM test)
Madhavadas S 2017 [37]	Sprague-Dawley rat pups	Male	Aqueous extract of Cinnamomum zeylanicum	8 (two groups at 2 and 10 months of age, each group divided into four subgroups Control, Control + Cinnamon Extract, Monosodium L-glutamate, Monosodium L-glutamate + Cinnamon Extract)	8	50 mg/kg	MSG induced AD	oral	20 weeks	Increase GSK-3β and inhibit cholinesterase activity, and increase neuron count	Barnes test (spatial learning and memory)	Positive effects on learning ability (Barnes test)
Edalatmanesh MA 2018 [38]	Sprague-Dawley rats	NM	Cinnamomum zeylanicum extract	5 (Control, Streptozotocin, STZ + Cinnamomum Zeylanicum Extract 100 mg/kg, STZ + CZE200mg/kg, STZ + CZE400mg/kg)	10	100 mg/kg 200 mg/kg 400 mg/kg	Streptozotocin	oral	14 days	Increase in neural density	Y Maze (spatial learning and memory) MWM (learning memory and spatial memory)	Positive effects on Y Maze and MWM tests
Pham HM 2018 [57]	Drosophila melanogaster	Both	Cinnamaldehyde	4 (2 control groups (AD MAPT And AD AB 420), 2 Cinnamaldehyde groups (AD MAPT And AD AB 420))	235, 221, 221 242	16 mg/kg, 80 mg/kg, 400 mM	Overexpressing Amyloid Beta42 and Tau protein	oral	20 days	NM	RING test (short-term memory)	improvement of short-term memory (RING test)
Saeed M 2018 [39]	Wistar rats	Male	Cinnamaldehyde	7 (Control, Methamphetamine, Methamphetamine + Cinnamaldehyde 80 mg/kg, MA + C20 mg/kg, MA + C40	6	20 mg/kg 40 mg/kg 80 mg/kg	Methamphetamine-induced spatial learning and memory deficit	IP	7 days	Increase ERK1/2	MWM (learning memory and spatial memory)	Positive effects on cognition, spatial learning and memory improvement (MWM test)

				mg/kg, MA + Rivastigmine, C80 mg/kg)								
Pan Z 2020 [40]	Wistar rats	Male	Trans-Cinnamaldehyde	5 (Control young, control aged, Trans Cinnamaldehyde, Ellagic acid, ELA + CIN)	8	50 mg/kg	Aged-induced cognitive impairment	IP	30 days	Reduction of ROS, IL-1β and IL-6, and apoptotic factors	NOR (recognition memory) Barnes test (spatial learning and memory)	Positive effects on cognition (NOR and Barnes test)
Qubty D 2021 [51]	ICR Mice	Male	Cinnamon extract (Cinnamon cassia aqueous solution)	4 (control, traumatic brain injury model (TBI), Cinnamon, TBI + cinnamon)	10,11,10,12	10 µg/mL	TBI by 70-g weight drop TBI device	Oral	2 weeks	Decrease neural loss in TBI	NOR (recognition memory) Y Maze (spatial learning and memory)	Improving in cognition and decrease memory loss, recognition and visual memory (NOR and Y-Maze)
Frydman-Marom A 2011 [3]	5XFAD mice	Male	Cinnamon Extract (Cinnamon bark aqueous solution)	3 (WT, transgenic, transgenic treated)	8,8,7	100 mg/ml	Transgenic Alzheimer's disease model mice	Oral	120 days	Decrease in 56 kDa Aβ	NOR (recognition memory)	Positive effect in Memory and Cognition (NOR)
Pandit C 2018 [41]	Albino Wistar rats	Male	Cinnamon + aqueous ethanol	8 (Room temperature (Control, Cinnamon, Pepper, Green tea), Cold temperature (Control, Cinnamon, Pepper) Green tea,	10	250 mg/kg	Normal	Oral	7 days	Decrease MDA, no change in SOD and catalase	NOR (recognition memory)	Cognitive impairment can be controlled by it cinnamon have effective role on recognition Memory (NOR)
Kazerouni A 2020 [52]	NMRI mice	Male	Cinnamaldehyde	6 (Control group, Cinnamaldehyde 12.5 mg/kg + scopolamine, Cinnamaldehyde 25 mg/kg + scopolamine, Cinnamaldehyde 40 mg/kg + scopolamine, Cinnamaldehyde 100 mg/kg + scopolamine, Cinnamaldehyde 100 mg/kg)	8 8 8 7 8 8	12.5 mg/kg, 25 mg/kg, 40 mg/kg 100 mg/kg	Scopolamine induced	Oral	10 days	NM	Passive avoidance test (learning and memory)	Cinnamaldehyde (100 mg/kg) had a significant positive effect on memory retrieval deficit (passive avoidance test) but no significant change in other doses.
Do J 2020 [53]	5XFAD Transgenic Mice	Both	Trans-Cinnamaldehyde + in saline (0.9% NaCl)	4 (vehicle-treated wild-type (WT), TCA-treated WT, vehicle-treated 5XFAD, TCA-treated 5XFAD	15,8,15,12	30 mg/kg	5XFAD Transgenic Mice	IP	8 weeks	Reduced Aβ deposition	MWM (learning memory and spatial memory) Passive avoidance test (learning and memory)	TCA improved cognitive impairment and Memory (Morris Water Maze and Passive avoidance test)
Zhang L 2016 [54]	ICR mice	Male	Trans-Cinnamaldehyde	6 (Control, TCA 50 mg/kg, LPS, LPS + TCA 12.5 mg/kg, LPS + TCA 25 mg/kg and LPS + TCA 50 mg/kg).	6-7	12.5 mg/kg 25 mg/kg 50 mg/kg	LPS-induced	I.P	28 days	Decreased LPS-induced morphological changes, IL-1β, and NO production	MWM (learning memory and spatial memory) NOR (recognition memory)	TCA improved impaired recognition memory (50 mg/kg) and spatial reference memory (25 and 50 mg/kg) (MWM test, NOR) other doses showed no significant changes.
Zhao Y 2019 [55]	Double Knockout Mice(PS cDKO mice)	Both	Trans-cinnamaldehyde	6 (WT, WT + TCA, cDKO, cDKO + TCA, cDKO + TP, cDKO + TCA + TP)	15	240 ppm	Double Knockout Mice (PS cDKO mice)	IP	60 days	Reversed abnormal synaptic proteins and tau hyperphosphorylation	NOR (recognition memory) MWM (learning memory and spatial memory) Y Maze (spatial learning and memory) FC (learning)	TCA improved recognition memory deficit in PS cDKO but not for WT (novel object recognition task) TCA also improved spatial and associative memory in PS cDKO group (MWM test, probe trial, Y Maze, and fear conditioning (FC) task)
El-ezz A 2018 [17]	Adult Swiss albino mice	Male	Trans-cinnamaldehyde phosphate-buffered saline (PBS)	4 (control, LPS, curcumin, and (Trans-cinnamaldehyde	20	50 mg/kg	LPS-induced	I.P	7 days	Activated Nrf2 and decreased A β accumulation and anti-apoptotic effect	MWM (learning memory and spatial memory) ORT (non-spatial memory)	Trans-cinnamaldehyde showed a positive effect on spatial (MWM test and probe test) and non-spatial memory (NOR)

NM (not mentioned), IP (intraperitoneal), Aβ/AB (Amyloid-Beta), ICR (institute of cancer research), MWM (Morris water maze), WT (Wild type), LPS (Lipopolysaccharide), TCA (Trans-Cinnamaldehyde), NOR (Novel Object Recognition), AD (Alzheimer's disease), CNMA (Cinnamaldehyde), ROS (reactive oxygen species), SOD (superoxide dismutase), GSH (glutathione), AchE (acetylcholine esterase), thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), Glial fibrillary acidic protein (GFAP), nuclear factor erythroid 2-related factor (Nrf2), microtubule-associated protein tau (MAPT), traumatic brain injury model (TBI), protein kinase B (Akt), extracellular signal-regulated kinase (ERK), glycogen synthase kinase 3-beta (GSK-3β), rapid iterative negative geotaxis (RING)

shown in Figure 1. Finally, 40 studies met the criteria and were included in the quality assessment and systematic review.

3.2. Study characteristics

These 40 studies of interest consisted of three categories; *in vivo* (n = 33) (Table 2), *in vitro* (n = 5) [27–31] (Table 3), and clinical trial (n = 2) [32,33] (Table 4). These studies were published between 2011 and 2021. Seventeen in vivo studies were on rats [15,34–49], 15 articles were conducted on mice [3,12,17,20,50–56], and one was on the common fruit fly (Drosophila melanogaster) [57]. On the other hand, for clinical trial studies, one was done on adolescents (ranging between 12 to 14 years) [32], and the other one was done on adults (60 y or older) [33]. Among the *in vitro* and *in vivo* studies, sixteen used the cinnamon extract /cinnamon powder [3,30,32,33,35–38,41–44,46,47,51,58–60], while others used different components of cinnamon (n = 22) [12,15,17,20,27–29,31,34,39,40,45,48–50,52–57,61]. The route of administration for animal models was mostly oral (n = 19) and intraperitoneal injection (n = 13); for clinical trials, both were done orally. The genders of animal models were mostly male (n = 24) and others were both male and female (n = 5) or not mentioned in the studies (n = 4). The outcomes for *in vitro* studies were measured via a diverse range of behavioral tests such as the Water Morris Test (WMT), Y maze, T Maze, Novel Object Recognition (NOR), Barnes Maze, Passive avoidance, and Open field. Most studies for cognitive function (memory and learning) deficit models used different chemical substances, including Streptozotocin (n = 5), Aluminum Chloride (n = 2), and LPS (lipopolysaccharide = 2), while other models were transgenic or other techniques [3,12,15,17,20,34–40,42,43,45–49,51–55,57–61]. Some used normal models for their studies [41,44,50,56].

3.3. Systematic review

Among all the 40 included studies, 18 were done with cinnamon, cinnamon extract, or cinnamon powder [3,30,32,33,35–38,41–44,46,47,51,58–60], while 22

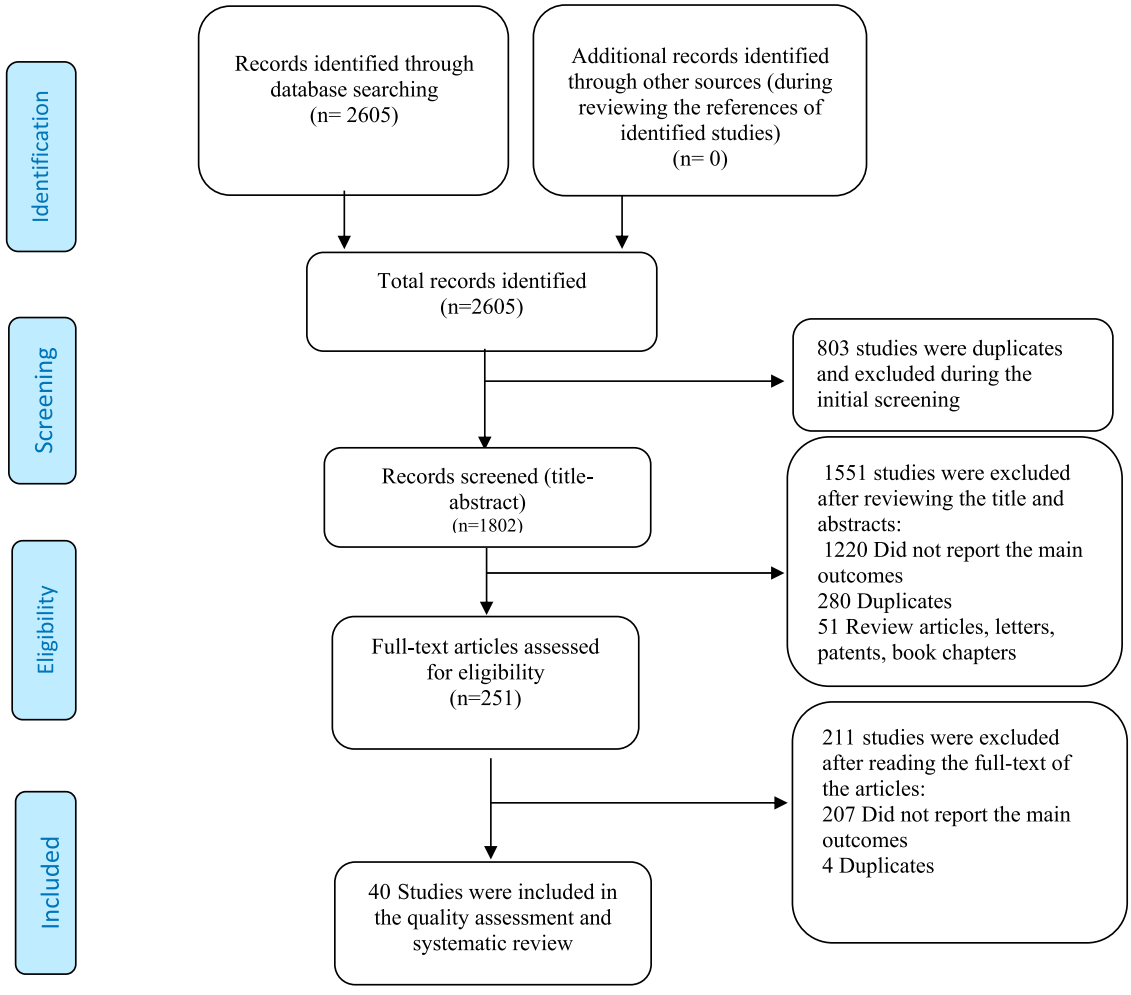

Figure 1. PRISMA Flowchart of the literature search and strategy for selecting a relevant document.

Table 3. Characteristics of included *In vitro* studies on the effects of cinnamon/its components on cognitive function (learning and memory).

Author (year)	Cell line	Cinnamon/ component	The concentration of Cinnamon/ component	Result
Emamghoreishi M 2019 [28]	Human SHSY5Y neuroblastoma cell	Cinnamaldehyde	15 μM, 20 μM, 23 μM, 25 μM	Cinnamaldehyde in all doses significantly reversed Aβ neurotoxicity
George RC 2013 [27]	The PCR amplified product was cloned into a pET28 vector and expressed in Escherichia coli strain BL21 (DE3)	Cinnamaldehyde	110 μM	Cinnamaldehyde significantly inhibited tau aggregation
Kang YJ 2016 [30]	APP-CHO cells	Methanol extract from cinnamon bark	4 μg/mL, 20 μg/mL, 50 μg/mL, 100 μg/mL (However cell viability significantly decreased by treatment with 100 μg/mL and therefore non-cytotoxic concentrations were evaluated)	Cinnamon bark extract inhibited Aβ40 production in APP-CHO cells (50 μg/mL dose significantly reduced the secreted Aβ40 in APP-CHO cells)
Fu Y 2017 [31]	Immortalized BV2 murine microglial cell line (LPS induced) & Rat pheochromocytoma PC12 neuronal cell line	Trans-cinnamaldehyde (reconstituted in DMSO)	10 μM	Reduced neural death and effective against neurodegenerative disorders
Bai L 2016 [29]	Human neuroblastoma cell lines (SH-SY5Y APP which expresses wild type Aβ precursor protein, SH-SY5Y APP SW, which expresses the Swedish mutation of APP, SH-SY5Y Neo, that are blank cells)	Cinnamaldehyde	100 μM	Cinnamaldehyde inhibited Aβ aggregation in all three types of cell lines and increased cell viability in APP and APPsw cell lines but not in Neo cell line

μM (micromolar), APP-CHO (amyloid precursor protein-Chinese hamster ovary), LPS (Lipopolysaccharide), Aβ (Amyloid-Beta)

studies used components of cinnamon such as eugenol, cinnamic acid, or cinnamaldehyde [12,15,17,20,27–29,31,34,39,40,45,48–50,52–57,61]. The effects of these compounds were assessed on cognitive function (memory and learning) for *in vivo* studies (n = 33), memory for clinical articles (n = 2) and Amyloid-Beta (n = 3), tau aggregation (n = 1) and neural survival (n = 1) for *in vitro* studies. All the animal studies used rats or mice except one that used Drosophila melanogaster [57].

3.3.1. Cinnamon (extract, powder, etc.)

Among all 40 included documents, 18 studies used cinnamon as the main compound. 2 of them were clinical trials, one was *in vitro*, and others were *in vivo* studies (n = 15).

3.3.1.1. Clinical studies. One clinical study on adolescents showed a positive effect on memory using Cinnamon chewing gum for 40 days [32], while the other reported no significant changes in memory using cinnamon administered orally (single dose/2 g) [33].

3.3.1.2. **In vitro** *studies.* The only *in vitro* study that used methanol extract from cinnamon bark positively inhibited the Amyloid-Beta 40 production at a dose of 50 μg/mL [30].

3.3.1.3. **In vivo** *studies.* There were variations across the *In vivo* studies regarding dosages of administered cinnamon, route (IP/oral) and duration of administration, and type of behavioral test. In general, most *In vivo* studies reported a positive effect on cognitive function (learning and memory) using a variety of behavioral tests like MWM, Y Maze, and NOR tests [3,35–38,41–43,46,47,51,58–60]. Although there were some exceptions, Vahidi et al. (2012) reported that 250 mg/kg and 500 mg/kg of cinnamon decreased learning and memory [44]. All behavioral tests showed positive effects of cinnamon except two studies showing no difference between the control and cinnamon group in the passive avoidance test in three doses of 100, 200, and 400 mg/kg of cinnamon zeylanicum alcoholic extract [47,58]. Overall, cinnamon positively affected every two subcategories of cognitive function.

3.3.2. Cinnamon's components

Twenty-two remaining studies used components of cinnamon such as eugenol [15,34,45,49,56], Cinnamic acid, trans-cinnamic acid [12,20], cinnamaldehyde, and trans cinnamaldehyde [17,39,40,48,50,52–55,57,61] as a target compound. Four of these studies investigated the effects of cinnamon's components *in vitro*, and others were *in vivo*. There was no clinical study using cinnamon's component.

3.3.2.1. **In vitro** *studies.* All four *in vitro* studies reported a positive outcome in a wide range of dosages (10, 15, 20, 23, 25, 100, and 110 μM). Two studies showed an inhibiting effect of Cinnamaldehyde on

Table 4. Characteristics of included human studies on the effects of cinnamon/its components on cognitive function (memory and learning).

Author (year)	Type of Study	Study population (groups)	A/C	Sample size	Gender	Age	Cinnamon/ component	Route of exposure	Duration of consumption	Dosage of cinnamon/ component	Memory test	Results
Rajan U Katherina 2012 [32]	Clinical trial	2 (control and experimental)	Adolescent	30 (15 each)	Both	12-14 y	cinnamon chewing gum	Oral/ chewing gum	40 days	NM	PGI memory assessment scale	Positive effects on memory
Lee MS 2014 [33]	Clinical trial	4 (Placebo, cinnamon, turmeric, turmeric + cinnamon)	A	48	Both	60 y or older (median 71-75)	cinnamon	Oral	Single-dose	2g	Modified N-back working memory test	No change in working memory

A/C (adults or children), NM (not mentioned)

Amyloid β [28,29], two reported an increase in neural survival using Trans-Cinnamaldehyde and Cinnamaldehyde [29,31], and one reported the inhibiting effects of cinnamaldehyde on *tau* aggregation [27].

3.3.2.2. **In vivo *studies.*** There were variations across the *In vivo* studies in terms of dosages of administered cinnamon components, route (IP/oral/olfactory) and duration of administration, and type of behavioral test. All included *in vivo* studies showed positive effects of cinnamon's components (eugenol, cinnamic acid, or cinnamaldehyde) on learning and memory [12,15,17,20,34,39,40,45,48–50,52–57,61]. These components' results were mostly positive in animal studies, except for some studies reporting no significant effect of Cinnamaldehyde and Eugenol in the MWM test nor passive avoidance test in some doses (10, 12.5, 20, 25 30,40, 100 mg/kg) [48,52,54,56,61]. According to this systematic review, eugenol has cognitive protective effects due to its general effects such as antioxidant, inhibition of amyloid plaque and anti-acetylcholinesterase. In addition, cinnamaldehyde and trans-cinnamaldehyde with anti-apoptotic, anti-inflammatory effects, improving insulin and nitric oxide signaling also exert protective effects against cognitive impairment [60]. It seems that the satisfactory results of cinnamon in improvement the cognitive function is due to the various mechanisms by various constituent ingredients that are all available in cinnamon.

3.3.3. Dose dependency

No dose dependency was found in the studies, so in some studies, the positive effects were found in lower doses [44, 47,58], and in others, it was reported in higher doses of cinnamon or its components [48,50,52].

4. Discussion

We systematically sought to review cinnamon's effect on Cognitive function (learning and memory). Moreover, this study showed that cinnamon could have a positive role in improving these factors. Studies that reported the positive effect of cinnamon and its components all passed the quality test, and their evidence is as strong as others. For one study that reported the negative effect of cinnamon, a quality assessment was also done, and 100% of the checklist items were approved. There were many variations across the included studies in our systematic review. For example, included studies had a wide range of duration of exposure and different dosages of cinnamon/its components. The ineffective result of some studies may be due to the short duration of their experiment or the lower dosage of cinnamon/its

components. On the other hand, the negative effects reported in some studies may be due to high doses of cinnamon and its toxic effects. Different routes of administration may also be a reason for different outcomes due to the lesser absorption in the oral route compared to intraperitoneal injection [62].

The other important factor causing diversity in results might be the administration of various components. For instance, most of the results for eugenol (a component found in cinnamon) were reported as positive, while the results for cinnamon extract were mixed.

Cinnamon and its bioactive compounds can exert its potential neuroprotective effects via different mechanisms. Here we explain some of the major molecular mechanisms that might justify the behavioral results we concluded in this systematic review:

It is known that cinnamon has antioxidant properties [63]. It can possess neuroprotective effects by interfering with multiple oxidative stress pathways [7]. In addition, the compound can be used to scavenge lipid peroxidation byproducts [27]. The oxidative stress hypothesis states that the brain tissue is highly sensitive to oxidative stress due to the low capacity of antioxidant defense, which can lead to Alzheimer's disease [64]. Many studies showed that different extracts of cinnamon [7,43,47] as well as the major active components of cinnamon essential oil, cinnamaldehyde [29,48,50], trans-cinnamaldehyde [31,40,54], cinnamic acid [12,65] and eugenol [34,56] inhibited the brain's oxidative stress process and can improve Alzheimer's pathology.

The mitochondrial cascade hypothesis explains that mitochondria dysfunction causes an increase in ROS and contributes to Amyloid – β formation, which can be improved by cinnamaldehyde [18,64]. On the other hand, cinnamic acid also had potential antioxidant properties due to the presence of vinyl fragments [12].

Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) both play vital roles in the pathogenesis of Alzheimer's disease [64]. It has been suggested that the deficiency in memory, learning, and other clinical protests of Alzheimer's disease comes from a lack of acetylcholine (Ach) neurotransmitters [66]. In this disease AChE level decrease, causing an increase in the BuChE level resulting in the misbalanced ratio of Ache/BuChE, which leads to deficiency in Ach level [64]. Some studies have considered this hypothesis a mechanism to work on; Cinnamon [36], cinnamaldehyde [48] and eugenol [34] were effective in these pathways by reducing AchE levels. Accumulation of extracellular Amyloid – β (amyloid plaque) and Tau protein are known to cause neural cell destruction [64]. Cinnamon and its components; cinnamaldehyde and eugenol inhibit Aβ-induced neurotoxicity. It is reported that cinnamon can interact with Aβ peptide in the first stage of its self-aggregation and inhibit that process [7]. Further, it reduces tau aggregation and Aβ oligomerization in cell culture and an AD animal model [3]. Also aqueous extract of Ceylon cinnamon reported to inhibit tau accumulation by prevention of assembly of free tubulins into microtubules in human brain [7].

Although Tau protein accumulation is doubtlessly linked to Alzheimer's disease, it is unknown what mechanism begins this extremely soluble protein aggregation in vivo [67]. In vitro, Tau can be made to generate fibrillar filaments by oxidizing its two cysteine residues. Ironically, cinnamaldehyde prohibits oxidation by binding to these two residues of amino cysteine on the Tau protein [27].

Interestingly increase in Tau phosphorylation is attributed to the activation of GSK-3β itself [27]. Furthermore, cinnamon/cinnamaldehyde also increases phosphorylated GSK-3β and neuron number in the hippocampus area of transgenic rats model of Alzheimer's disease [7,50]. However, the effect might be biphasic, with a positive effect at higher doses (45, 50, 100 mg/kg) and a negative effect at lower doses (12.5,25,30 mg/kg) that has been reported in our systematic review [50].

The inflammation hypothesis also states that by activating different kinds of cytokines, the microglial cells can cause an inflammatory response [68]. Cinnamaldehyde/trans-cinnamaldehyde has been reported to have anti-neuroinflammatory effects by reducing NO production [54], IL-1ß, TNF- α, and inhibiting the NF-kB pathway [14]. Moreover, elevated levels of inflammatory markers, such as TNFα, IL1-β, and other cytokines, that have been increased in AD play a crucial role in insulin signaling impairment by inhibition of serine phosphorylation of insulin receptor signaling [69]. Brain insulin signaling impairment is linked to alteration of PI3K-Akt signaling [70]. Cinnamaldehyde decreased AD pathology partly by increasing the phosphorylated forms of hippocampal Akt, ERK, and GSK-3β [50]. In the brain, the PI3K-Akt signaling of insulin plays a vital role in neuronal survival as well as synapse formation and preservation [71]. PI3K-Akt signaling is a key pathway that inhibits GSK3β by phosphorylating the serine 9 that in turn decreases tau phosphorylation [69].

BDNFs (brain-derived neurotrophic factors) are a neurotrophin family of growth factors important in neural survival, synaptic plasticity, and morphology [72]. Cinnamaldehyde, along with cinnamon's metabolite, sodium benzoate, and eugenol, can induce the

expression of BDNF [73–75]. As one of the cinnamon components, eugenol can antagonize the aluminum-caused memory deficit [55]. It can also increase the dendritic complexity of neurons in the dentate gyrus and cornu ammonia [56]. Besides, it increases SOD (superoxide dismutase) activity and can decrease and destroy free radicals and ROSs the main cause of neurological diseases such as Alzheimer's [15,42]. Furthermore, it is assumed that it can pass through the BBB (blood–brain barrier) and have an inhibitory effect on cholinesterase, which is effective in Alzheimer's disease management [15]. Also, eugenol significantly reduced amyloid plaque, especially with lower doses (0.01 mg/kg) [15]. In one study, it has been reported that phenylpropanoid compounds isolated from cinnamon, targeted β-secretase (an enzyme that is essential for myelination and it also is crucial to amyloid-beta formation process) [76] and reduced Aβ production by inhibiting its production in Chinese hamster [30].

5. Limitations

Some of the included studies provided preliminary information for measuring memory and learning, and unfortunately, we could not provide a meta-analysis due to the lack of precise data. Furthermore, because of the usage of different components of cinnamon and different duration of exposure to these compounds, we could not investigate the dose dependency of these components. Additional and larger studies considering other components of cinnamon could produce valuable results in this context. Moreover, due to the intertwined nature of learning and memory, we needed to specify the effects of cinnamon or its components on learning and memory separately. Also, because of the limited number of clinical studies in this field, it is necessary to perform more clinical studies on this subject. It is also beneficial that in vivo studies in this field propose the probable mechanism of cinnamon affecting the brain to specify the related pathways more precisely.

6. Conclusion

This systematic review revealed that cinnamon and its components (eugenol, cinnamic acid, cinnamaldehyde, etc.) could affect memory and learning by decreasing Amyloid plaque in the hippocampus and phosphorylation of tau-protein. This function is accomplished by different mechanisms and pathways including antioxidant, anti-inflammatory, and anticholinesterase activity as well as neurotrophic effect, neural maintenance and insulin signaling improvement. Most of the in vivo studies also confirmed the significant positive result in all two mentioned fields of cognitive function (memory and learning) using behavioral tests. Furthermore, all in vitro studies somehow showed significant positive results after using cinnamon and cinnamaldehyde by decreasing neural death and lowering Tau or Amyloid-β accumulation.

Availability of data and material

On formal and logical requests, the datasets are accessible from the corresponding author.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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