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Research report

The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies

S.D. Voulgaropoulou[a,*], T.A.M.J. van Amelsvoort[a], J. Prickaerts[a], C. Vingerhoets[a,b]

[a] Department of Psychiatry & Neuropsychology, Maastricht University, Minderbroedersberg 4-6, 6211 LK Maastricht, The Netherlands
[b] Department of Radiology & Nuclear Medicine, Amsterdam University Medical Centre, Location AMC, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands

HIGHLIGHTS

- Animal studies show beneficial effects of curcumin on molecular and behavioral level.
- Clinical studies are mixed regarding curcumin's effects on cognitive deficits.
- Ways to improve curcumin's bioavailability are required.
- Homogenized clinical trials are needed to understand curcumin's therapeutic potential.

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ABSTRACT

Alzheimer's disease constitutes a growing cause of cognitive impairment in aging population. Given that current treatments do not produce the desired therapeutic effects, the need for finding alternative biological and pharmacological approaches is critical. Accumulating evidence suggests inflammatory and oxidative stress responses as potential causal factors of cognitive impairments in Alzheimer's disease and healthy aging. Curcumin has received increased interest due to its unique molecular structure that targets inflammatory and antioxidant pathways as well as (directly) amyloid aggregation; one of the major hallmarks of Alzheimer's disease. Therefore, this review summarizes preclinical and clinical findings on curcumin as a potential cognitive enhancer in Alzheimer's disease and normal aging. Databases used for literature searches include PubMed, EMBASE and Web of Science; in addition, clinicaltrials.gov was used to search for clinical studies. Overall, animal research has shown very promising results in potentiating cognition, both physiologically and behaviourally. However, human studies are limited and results are less consistent, complicating their interpretation. These inconsistencies may be related to differences in methodology and the included population. Taking into account measurements of important inflammatory and antioxidant biomarkers, optimal dosages of curcumin, food interactions, and duration of treatment would increase our understanding on curcumin's promising effects on cognition. In addition, increasing curcumin's bioavailability could benefit future research.

1. 1.Introduction

Neurodegeneration is a hallmark feature of many age-related devastating diseases. The most frequent neurodegenerative disease is Alzheimer's disease (AD), which accounts for 60–70% of cases with dementia (Duthey, 2013; Erkkinen et al., 2018). The symptoms of AD are characterized by faltering cognitive abilities followed by impaired social and behavioural functioning. The main histopathological features of AD are amyloid-β (Aβ) plaques, caused by changes in proteolytic processing of amyloid precursor protein (APP), and neurofibrillary tangles (NFTs) caused by hyper-phosphorylation of the tau protein (Hardy & Selkoe, 2002). According to World Health Organization's (WHO) report, 35.6 million people worldwide suffer from this disease and as the lifespan of elderly population increases it is estimated that the frequency will be doubled by 2030 and tripled by 2050 (Duthey, 2013). At present, pharmacological treatments to prevent or cure the cognitive decline are lacking. Even though the existing cognitive enhancers approved for AD, such as donepezil and galantamine, may postpone cognitive deterioration, many patients do not respond to the treatment, the beneficial effect is temporal and accompanied by a number of adverse effects (Husain & Mehta, 2011).

The lack of effective pharmacotherapy has led researchers to seek

* Corresponding author.
E-mail address: s.voulgaropoulou@maastrichtuniversity.nl (S.D. Voulgaropoulou).

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alternative approaches in order to treat or prevent AD and more neurobiological underpinnings are being discovered. Accumulating evidence suggests neuroinflammation, oxidative stress, mitochondrial dysfunction or autophagy as potential etiologies for AD (Amor et al., 2014; Amor et al., 2010; Guo et al., 2018; Kim et al., 2015). For example, it has been reported that in populations with chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), the risk for developing AD is significantly lower (Breitner et al., 1995; Stewart et al, 1997). Although recent studies regarding the effect of NSAIDs on AD have yielded both negative and beneficial results (Zhang et al., 2018; Miguel-Álvarez et al., 2015), one major limitation for the use of NSAIDs is the gastrointestinal toxicity caused by inhibition of cyclooxygenase (Lim et al., 2001). Therefore, the urgency of finding new, safer, (more) effective pharmacological strategies is commonly accepted. Epidemiological studies indicate that natural antioxidant agents, such as polyphenols, fatty-acids or vitamin-rich aliments, may delay the occurrence of neurodegenerative diseases, however, randomized controlled clinical trials are absent to confirm the protective or therapeutic efficacy of such molecules (Bastianetto & Quirion, 2004; Stab et al., 2012).

Curcumin is an active hydrophobic polyphenol extracted from the rhizomes of herb *Curcuma Longa* Linn, also known as turmeric, which belongs to the family of zingiberaceae. Traditionally, curcumin has been used as a remedy for many ailments in India and China (Ghosh et al., 2015). Modern medicine has shown that curcumin exhibits a wide variety of biological and pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, chemoprotective properties, due to its ability to modulate numerous signaling molecules (Gupta et al., 2012; Hewlings & Kalman, 2017). Its anti-inflammatory activity can be attributed to the suppression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) enzymes via down-regulation of nuclear factor kappa B (NF-κB) as well as inhibition of several inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a) or interleukin (IL) -1, -2, -6, -8, and -12 (Jurenka, 2009). Curcumin's ability to scavenge free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), provides its antioxidant capacity (Alisi et al., 2018). Multiple studies in rodents and humans have shown that curcumin crosses the blood brain barrier (BBB) (Dende et al., 2017; Mishra & Palanivelu, 2008; Reddy et al., 2018). However, its main drawback is the low bioavailability due to poor solubility, low absorption, rapid metabolism, and rapid excretion (Gupta et al., 2012). Much effort has been made attempting to overcome this issue and new formulations have been developed, including liposomal encapsulation, nanoparticles, powder form, micellar form, emulsions, co-administration with other substances, or separate administration of its constituents. Curcumin is considered to be a safe compound, thus suitable for daily dietary use as established by the Joint Nations and World Health Organization Expert Committee on Food Additives (JECFA) (JECFA, 1996). Therefore, many curcumin-based products are currently freely available (Jamwal, 2018).

Both the pleiotropic and favorable safety profile of curcumin make it a promising compound for use in complex diseases, such as AD and associated cognitive decline. Novel approaches advocate that these cognitive deficits may be caused by abnormalities in multiple signaling pathways; especially inflammatory and oxidative stress mediated pathways. Thus, multi-target compounds could effectively combat cognitive deficits. Since curcumin interacts with numerous molecules involved in these pathways, it may be a promising compound for treatment/prevention of cognitive decline. Therefore, the aim of this systematic review is to provide an overview of pre-clinical and clinical studies that have examined how curcumin affects cognitive performance in AD and non-pathological aging.

2. Methods

This systematic review was conducted according to the established PRISMA guidelines (Liberati et al., 2009). A literature search was conducted in PubMed, EMBASE and Web of Science to obtain both preclinical and clinical trials. In addition, ClinicalTrials.gov was searched for human studies. The following keywords were used: ((((((curcuma [MeSH Terms]) OR curcumin [MeSH Terms]) OR curcuma) OR curcumin)) AND (((((((cognitive) OR cognition) OR cognitive disorders [MeSH Terms]) OR "cognition disorders") OR "Alzheimer's disease") OR "aging") OR neurodegenerative diseases [MeSH Terms])). Separate searches were applied for clinical and pre-clinical studies using the respective filters. Retrieved articles were imported to EndNoteX8. All articles were independently screened for, duplicity, eligibility by author SV and checked by author CV.

Inclusion criteria were: I) original research, II) published in English, III) use of any form of curcumin as the main pharmacological challenge or treatment (including cases in which a compound was added in order to increase curcumin's bioavailability), IV) use of validated cognitive tests (either for animals or humans) and V) published before June 2018. Articles were excluded if I) the study did not evaluate AD or aging, II) no cognitive or behavioral tests were used III) curcumin was used as a positive control or as adjunctive therapy IV) only abstract was available V) the article was a review, a case report, an *in-vitro*, *in-silico* or a non-randomized clinical study.

In total the search yielded 819 articles of which 38 met inclusion criteria (Fig. 1). Six hundred forty-five preclinical articles were retrieved of which 32 were included after full text screening. One hundred seventy-four human studies were identified of which 5 articles were deemed for inclusion after the final screening. In total, 21 preclinical studies evaluating AD and 11 studies examining healthy aging were included. Aging was included since not only is aging the prime risk factor for the development of AD but also the majority of clinical trials has been conducted in a healthy or mildly cognitive impaired geriatric population. Therefore, it was considered essential to include studies examining aging due to their high translational value. Study characteristics are depicted in Table 1. Concerning the clinical trials, three of the studies evaluated curcumin on a healthy geriatric population, while the remaining two studies used patients with mild to moderate Alzheimer's disease to test curcumin's efficacy on cognition.

3. Results

3.1. Preclinical studies

3.1.1. Alzheimer's disease (AD)

AD is characterized by the presence of intraneuronal NFTs and extracellular Aβ plaques, leading to neuronal loss and brain atrophy (Hardy & Selkoe, 2002). Cognitive decline, caused by the accumulation of Aβ plaques and NFTs, is evident in an anterior-posterior manner, from memory and executive functioning to learning deficits. However, the underlying mechanism inducing these protein aggregates remains elusive. Currently, no pharmacological treatment is available to ameliorate the symptoms of the disease. Curcumin binds to Aβ plaques, reducing their neurotoxicity and initiating their degradation (Lim et al., 2001). Therefore, it is considered a promising therapeutic agent for altering the cognitive symptoms of AD, as evident by the excess of preclinical studies examining its efficacy.

3.1.1.1. Natural curcumin. Natural curcumin, the substance obtained without chemical modification, has been studied extensively. Ishrat et al. (2009) explored the effects of natural curcumin (80 mg/kg) on cognitive performance using intracerebroventricular–streptozotocin (ICV–STZ) infused rats. Streptozotocin (STZ) is a diabetogenic substance that inhibits the neuronal insulin receptor and leads to cholinergic deficiency exerting cognitive impairments along with oxidative stress. Therefore, ICV–STZ is used as a model for sporadic dementia of the Alzheimer's type (SDAT). Three weeks of oral curcumin treatment after STZ induction significantly improved spatial learning and memory compared to the vehicle treated group. However, both STZ

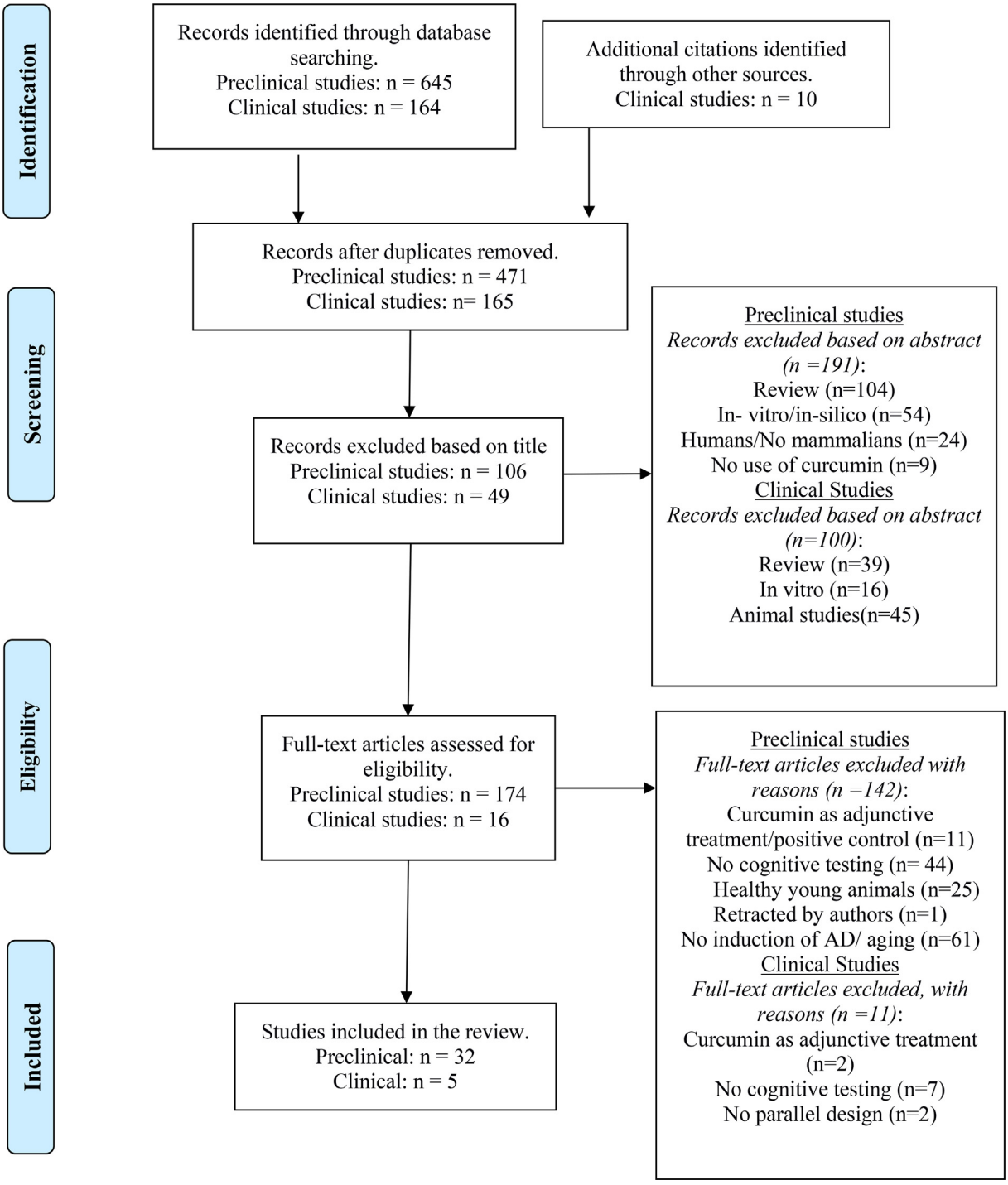

Fig. 1. Flow diagram of the systematic review process.

infused groups showed poorer performance compared to the sham controls. Furthermore, no difference was observed between sham groups receiving curcumin or vehicle, indicating that curcumin is effective in obstructing STZ induced cognitive impairment but does not affect cognition in healthy rodents.

Using a comparable model, Agrawal et al. (2010) evaluated the preventive and the therapeutic effect of 200 mg curcumin on SDAT. Curcumin was administered orally 14 days prior to disease induction or 6 days after its induction. Administration of curcumin enhanced memory performance in Morris Water Maze (MWM) over time in both conditions. Additionally, levels of oxidative stress, acetylcholine and insulin were restored after administration of curcumin.

Similarly, Awasthi et al. (2010) evaluated the preventive role of curcumin at oral doses of 10, 20 and 50 mg/kg, starting the same day as the induction of SDAT. To evaluate the therapeutic potential, curcumin was also administered at 25 and 50 mg/kg for 7 days after the induction of the disease. Curcumin prevented memory deficits at dosages of 20 and 50 mg/kg, while administration of 25 and 50 mg/kg of curcumin reversed memory impairments in a dose dependent manner with the higher dose exerting more beneficial effect. Furthermore, curcumin restored cerebral blood flow, oxidative stress and acetylcholinesterase activity. Another research group assessed the protective role of curcumin at a dose of 300 mg kg/day, i.p, (Isik et al., 2009). Additionally, the level of insulin-like growth factor-1 (IGF-1), a growth factor that

Table 1
Summary of the included pre-clinical studies.

Study	Duration of treatment	Study design, Dose & Route of administration	Species (N)	Cognitive Measurements	Primary Objective	Main results
Alzheimer's disease						
Ishrat et al. (2009)	3 weeks	(1) Sham:$_1$operation + vehicle; (2) sham$_2$: operation + CUR (80 mg/kg, p.o); (3) STZ + vehicle, p.o; (4) STZ + CUR (80 mg/kg, p.o)	Male Wistar rats (N = 40; n = 10/group)	MWM, PA	The effect of curcumin on cognitive impairments and oxidative damage in ICV-STZ infused rats.	CUR counteracted ICV-STZ-induced alterations in cognitive and behavioral parameters and in markers of oxidative stress.
Agrawal et al. (2010)	1–14 days (pre-treatment) 14–20 days (post-treatment)	(1) Untreated group; (2) swimming control (no training); (3) vehicle treated group, p.o; (4) Sham group; (5) STZ group; (6) pre-treated CUR (200 mg, p.o) + STZ; (7) post-treated CUR 200 mg, p.o + STZ	Adult male Sprague–Dawley rats (N = 35; n = 5 per group)	MWM	The effect of curcumin on memory and insulin receptors in the brain.	Curcumin improved memory and restored insulin, cholinergic and oxidative stress markers.
Awasthi et al. (2010)	1–21 days(pre-treatment) 19–25 (post-treatment_	Pre-treatment: (1) Control group; (2) Sham group; (3) STZ group; (4) STZ + 10 mg/kg CUR; (5) STZ + 20 mg/kg CUR; (6) 50 mg/kg CUR, p.o. Post-treatment (1) STZ + vehicle; (2) STZ + 25 mg/kg CUR; (3) STZ + 50 mg/kg CUR, p.o	Adult male Swiss albino mice (n = 6–8 per group)	MWM, PA	The preventive and therapeutic effect of curcumin on memory, cerebral blood flow, oxidative stress and cholinergic levels.	Curcumin prevented and reversed spatial memory deficits in a dose dependent manner. Additionally, it improved cerebral blood flow, oxidative and cholinergic levels in the brain.
Isik et al. (2009)	10 days	(1) Sham group; (2) STZ + vehicle (0.5 ml, i.p); (3) STZ + CUR (300 mg/kg daily in vehicle, i.p)	Male Wistar rats (N = 24; $n_1 = 8$, $n_2 = 7$, $n_3 = 8$)	PA, MWM	The neuroprotective effect of CUR compared to ICV-STZ induced cognitive impairments.	Curcumin significantly improved behavioral and histological alterations resulting from ICV-STZ induction. Additionally, IGF-1 levels were elevated after administration of curcumin.
Samy et al. (2016)	3 months	(1) Sham group; (2) ICV-STZ + vehicle; (3) ICV-STZ + curcumin (80 mg/kg/day, p.o); (4) ICV-STZ + erythropoietin (500 IU/kg qod, i.p); (5) ICV-STZ + curcumin (80 mg/kg/day, p.o) & erythropoietin erythropoietin (500 IU/kg qod, i.p)	Male Wistar rats (N = 40; n = 8/group)	MWM, PA	The comparison of combined CUR and erythropoietin treatment against monotherapy in cognition.	Both combined and monotherapy reversed cognitive, biochemical and histological changes. However, curcumin demonstrated a better safety profile.
Bassani et al. (2017)	30 days	(1) Sham group; (2) STZ infused group; (3) STZ + CUR (25 mg/kg, p.o); (4) STZ + CUR (50 mg/kg, p.o); (5) STZ + CUR (100 mg/kg, p.o)	Male Wistar rats (N = 35; $n_1 = 7$, $n_2 = 7$, $n_3 = 6$, $n_4 = 8$, $n_5 = 7$)	OFT, OLT, ORT, EPM, Y-Maze	To examine the possibility that chronic administration of CUR may favor cognition of STZ induced rats and increase neuronal proliferation.	At high dosages curcumin might be able to prevent short term recognition but not spatial memory. No signs of neurogenesis were evident, but reduced neuroinflammation was observed.
Zhang et al. (2015)	7 days	(1) Sham group; (2) Aβ1-42 + saline; (3) Aβ1-42 + 50, (4) 100, and (5) 200 mg/kg, i.p. of curcumin respectively	Male Sprague Dawley rats (N = 40; n = 8 in each group)	Y-Maze, OFT, MWM	The modulating impact of curcumin on cognitive deficits after ventricular injection of amyloid-β1-42 (Aβ1-42).	Chronic CUR supplementation attenuated Aβ1-42 induced cognitive impairments and increased BDNF levels in the hippocampus.
Wang et al. (2013)	7 days	(1) Sham group; (2) $A\beta_{1-40}$ (10 μl) + vehicle (300 mg, i.p); (3) $A\beta_{1-40}$ + CUR (300 mg, i.p)	Male Sprague-Dawley rats (N = 48; n = 16/group)	MWM	To examine the protective effect of CUR on $A\beta_{1-40}$-induced cognitive deficits and explore whether CUR acts on collapsing response mediator protein-2 (CRMP-2).	Treatment with CUR significantly ameliorated cognitive impairments and moderated phosphorylation of CRMP-2 leading to hippocampal regeneration.
Yin et al. (2014)	7 days	(1) Sham group; (2) $A\beta_{1-40}$ + vehicle (300 mg/kg, i.p); (3) $A\beta_{1-40}$ + CUR (300 mg/kg, i.p)	Male Sprague-Dawley rats (N = 48; n = 16/group)	MWM	To explore the underlying mechanisms of curcumin for the treatment of AD.	CUR significantly improved spatial memory performance. CUR's mechanism of action could be related with suppressing hippocampal Nogo receptor expression and subsequently increasing axonal regeneration.
Frautschy et al. (2001)	2 months	(1) Control group, vehicle; (2) Aβ infused + vehicle (chow); (3) Aβ infused + CUR (500 ppm, chow)	Female Sprague-Dawley rats (N = 30; n = 10/group)	MWM	Protective activity of dietary curcumin against Aβ-induced neurotoxicity and cognitive deficits.	CUR prevented memory deficits and attenuated Aβ deposits as well as post-synaptic density (PSD)-95 loss.
Wang et al. (2011)	7 days	(1) Sham group + saline; (2)$A\beta_{1-40}$ + saline; (3) $A\beta_{1-40}$ + CUR (300 mg/kg/day, i.p)	Male Sprague-Dawley rats (N = 48; n = 16/group)	MWM	The effect of CUR on AD related cognitive deficits and cell apoptosis.	CUR significantly improved cognitive impairments and protected against neuronal apoptosis.

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Table 1 (*continued*)

Study	Duration of treatment	Study design, Dose & Route of administration	Species (N)	Cognitive Measurements	Primary Objective	Main results
Wang et al. (2014)	6 months	(1) APP/PS1 control group; (2) APP/PS1 + CUR (160 ppm); (3) APP/PS1 + CUR (1000 ppm) in diet, chow	Male mice (N = 33; n = 11/group)	MWM	To evaluate whether CUR can induce autophagy and attenuate cognitive impairments induced in APP/PS1 double transgenic mice model.	CUR improved memory in a dose depended manner and induce autophagy.
Jia et al. (2016)	14 days	(1) CUR solution; (2) CUR-Pos; (3) CUR-Tf/-Pos (15 mg, i.v); (4) CUR-Tet-1-Pos (15 mg, i.v); (5) CUR-Tf/Tet-1-Pos (15 mg, i.v); (6) $A\beta 1_{-42}$ induced control group + saline i.v; (7) sham control group	Male C57BL/6 mice (n = 8 per group)	MWM	The effect of different formulations of CUR on cognition in Aβ1-42 induced mice.	CUR-Tf/Tet-1-Pos and CUR-Tf-PO formulations demonstrated significant improvement after Aβ-induced memory and cognitive impairment. *In vivo* and *in vitro* results supported better bioavailability of Tf/Tet-1-Pos formulation.
Hoppe et al. (2013)	10 days	(1) Sham group; (2) sham + free CUR; (3) sham + CUR-loaded lipid-core nanocapsules (Cur-LNC group); (4) $A\beta_{1\text{-}42}$ infused group; (5) $A\beta_{1\text{-}42}$ infused + vehicle (6) $A\beta_{1\text{-}42}$ infused + blank lipid-core nanocapsules (B-LNC group), (7) i.c.v infused + free CUR; (8) Cur-LNC group) → 50 mg/kg/day CUR and 2.5 mg/kg/day Cur-LNC, i.p.	Male Wistar rats (n = 10–16/ group)	Y-Maze, NORT	To compare efficacy and bioavailability of free CUR versus Cur-LNC and identify potential mechanisms underlying curcumin's protection against $A\beta_{(1-42)}$ induced cognitive impairment.	Administration of curcumin in both formulations prevented behavioral impairments, neuroinflammation, as well as cell synaptic malfunctions triggered by Aβ induction. Nanoencapsuled curcumin demonstrated higher potency compared to free CUR.
Tiwari et al. (2013)	3 weeks	(1) Sham group; (2) Aβ untreated (2) Aβ + empty PLGA-NP-; (3), (4) Aβ + bulk Curcumin-Treated Group (0.5 and 20 mg/kg, i.p.) mg/kg); (5), (6) CUR-PLGA-NPs-Treated Group (0.5 and 20 mg/kg, i.p.)	Male Wistar rats (n = 6/group)	PA	Comparison between bulk CUR and CUR nanoparticles in hippocampal neurogenesis and cognition.	CUR-loaded nanoparticles at both doses and high dose of bulk curcumin ameliorate cognitive impairments and potentially increases neurogenesis in an Aβ rat model.
Ahmed et al. (2010)	5 days → short term & 20 days → long term	(1) Control group; (2) Ab induced group; (3), (4) curcuminoids 3 mg/kg and 30 mg/kg, i.p; (5), (6) curcumin, 3 mg/kg and 30 mg/kg, i.p; (7), (8) bisdemethoxycurcumin 3 mg/kg and 30 mg/kg, i.p; (9), (10) demethoxycurcumin 3 mg/kg and 30 mg/kg, i.p	Male, Sprague–Dawley rats (n = 8/group)	MWM	The effects of curcuminoid mixture and its individual constituents on spatial learning and memory in an amyloid-beta (Aβ) peptide-infused rat model of AD.	Individual curcuminoid components demonstrate more effective profile than the parent mixture on memory performance.
Ma et al. (2013)	4 months	(1) Wild-type animals; (2) Control hTau mice; (3) hTau + CUR -Longvida (500 ppm in chow)	Male & female C57Bl/6J mice (N = 24; n_1 = 9, n_2 = 7, n_3 = 8)	MWM, Y-Maze, NORT	The effect of dietary curcumin on NFTs accumulation and memory.	CUR supplementation enhanced cognitive performance in mice and reduced soluble tau aggregates.
Sundaram et al. (2017)	12 weeks	(1) WT normally fed; (2) WT Longvida 4 g/kg (0.8 g CUR/kg) in chow; (3) p25Tg normally fed; (4) p25Tg CUR Longvida 4 g/kg (0.8 g CUR/kg) in chow	Male & female C57BL/6 mice (N = 22; n_1 = 5, n_2 = 6, n_3 = 5, n_4 = 6)	8-arm radial maze	To investigate fundamental and behavioral effects of Longvida® on AD mice model.	Dietary Longvida improved cognitive functions and mitigated neuroinflammation as well as features of AD.
Yanagisawa et al. (2015)	6 months	(1) WT group; (2) Control group, APPswe/PS1dE9; (3) APPswe/PS1dE9 + free CUR; (4) APPswe/PS1dE9 + FmeC1; (5) APPswe/PS1dE9 + FmeC2 → 500 ppm in chow	Male & female C57BL/6 mice (N = 48; n_1 = 12, n_2 = 12, n_3 = 6, n_4 = 12, n_5 = 6)	MWM, Y-Maze	To compare free CUR, FmeC1 and FmeC2 for the treatment of AD.	FmeC1 showed superior efficacy in reducing cognitive deficits and Aβ aggregates compared to the other two formulations.
Okuda et al. (2017)	9 weeks	(1) SAMP8/TaSlc + vehicle; (2) SAMP8/TaSlc + PE859 (1 mg/kg/day, i.g); (3) SAMP8/TaSlc + PE859 (3 mg/kg/day, i.g)	Male SAMP8/TaSlc mice (N = 25; n_1 = 9, n_2 = n_3 = 8)	MWM, Y-Maze, Rotarod, Grip strength	To examine the efficacy of a new CUR derivative, named PE859 on an AD model.	Even though no significant differences were observed in behavioral testing, PE859 reduced Aβ1-40 aggregates.
McClure et al. (2017)	18 Weeks	(1) WT group; (2) 5XFAD, control; (3) 5XFAD + 5 mg/kg CUR, i.n	Male & female C57BL/6 mice (N = 30; n = 10/group)	Y-maze	To evaluate intranasal formulation of CUR for the prevention of AD.	Nebulized CUR prevented memory deficits and reduce formation of Aβ plaques.
Ageing						
Kumar et al. (2011)	6 weeks	(1) Vehicle control group; (2) D-gal (100 mg/kg, s.c.); (3) Galantamine (5 mg/kg, p.o.) + d-gal (100 mg/kg); (4) CUR (15 mg/kg, p.o.) + d-gal (100 mg/kg); (5) CUR (30 mg/kg, p.o) + d-gal (100 mg/kg, s.c); (6) CUR alone (30 mg/kg, p.o)	Male Laca mice (n = 12 per group)	MWM, EPM	To explore the possible protective role of curcumin against D-galactose-induced cognitive dysfunction, oxidative damage, and mitochondrial dysfunction in ageing mice.	All treatment groups showed improvement in cognitive and neurobiochemical markers. Locomotor ability remained unchanged.

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Table 1 (*continued*)

Study	Duration of treatment	Study design, Dose & Route of administration	Species (N)	Cognitive Measurements	Primary Objective	Main results
Nam et al. (2014)	10 weeks	(1) Control group + vehicle; (2) D-gal (100 mg/kg, s.c); (3) CUR (300 mg/kg, p.o) (4) D-gal (100 mg/kg, s.c) + CUR (300 mg/kg, p.o)	Male C57BL/6 mice (n = 10 per group)	MWM	The effects of CUR on learning and spatial memory in healthy and D-galactose-induced aged mice.	Curcumin protected against memory impairment induced by D-gal and increased neurogenesis in the hippocampus.
Banji et al. (2013a,b)	49 days	(1) Young rats + vehicle, p.o; (2) Aged rats + vehicle, p.o; (3) Young rats + D-gal (60 mg/kg, i.p); (4) Young rats + D-gal + CUR (20 mg/kg, p.o); (5) Young rats + D-gal + piperine (6 mg/kg, p.o); (6) Young rats + D-gal + CUR (20 mg/kg, p.o) + piperine (6 mg/kg, p.o); (7) Young rats + D-gal + CUR (40 mg/kg, p.o) + piperine (12 mg/kg, p.o)	Male Wistar rats (N = 36; n = 6 per group)	MWM	To compare effects of single and combined administration of CUR and piperine on aging.	Superior effect of combined compared to separate administration of CUR and piperine in cognitive and neurobiochemical changes related to aging.
Banji et al. (2013a,b)	56 days	(1) Young rats + vehicle, p.o; (2) Aged rats + vehicle, p.o; (3) Young rats + D-gal (150 mg/kg, s.c); (4) Young rats + D-gal + CUR (40 mg/kg, p.o); (5) Young rats + D-gal + piperine (7.5 mg/kg, p.o); (6) Young rats + D-gal + CUR (20 mg/kg, p.o) + piperine (7.5 mg/kg, p.o); (7) Young rats + D-gal + CUR (40 mg/kg, p.o) + piperine (15 mg/kg, p.o)	Male Wistar rats (N = 36; n = 6 per group)	EPM, Rotarod	To delineate the synergistic effect of curcumin and piperine in treating aging symptoms and to compare it with monotherapy.	Co-administration of CUR and piperine improved cognitive and motor D-gal induced impairment and reduced oxidative stress.
Banji et al. (2014)	63 days	(1) Control group + vehicle; (2) D-gal (150 mg/kg, s.c) + vehicle; (3) D-gal + CUR (50 mg/kg, p.o); (4) D-gal + hesperidin (10 mg/kg, p.o); (5) D-gal + CUR (50 mg/kg, p.o) + hesperidin (10 mg/kg, p.o); (6) D-gal + CUR (100 mg/kg, p.o) + hesperidin (25 mg/kg, p.o)	Wistar rats (Not mentioned)	MWM	To delineate the combination of CUR and hesperidin as compared to their individual administration for the treatment of D-gal induced cognitive impairments.	The mixture of CUR and hesperidin as well as individual administration minimized the behavioral impairments. The higher doses of the mixture reversed apoptosis, mitochondrial and oxidative damage.
Sun et al. (2013)	25 Days	(1) SAMR1 mice, as control (normal aging); (2) SAMP8 mice; (3) SAMP8 + CUR (20 mg/kg, i.g); (4) SAMP8 + CUR (50 mg/kg, i.g)	Male SAMP8 and SAMR1 mice (n = 22/group)	MWM	The effect of CUR on learning and memory in aging and its possible mechanisms.	Both dosages of CUR significantly improved cognition, normalized oxidative damage and enhanced synaptic plasticity. The higher dose displayed stronger effects.
Dong et al. (2012)	6 &12 weeks	(1) Control group; (2) CUR (480 mg/kg, in chow) → six weeks; (3) CUR (480 mg/kg, in chow) → twelve weeks	Male Sprague-Dawley rats (N = 45; n = 15/group)	OFT, Rotarod, social recognition test, MWM	To assess behavioral performance and hippocampal cell proliferation in aged rats after 6- and 12-week curcumin-fortified diets.	Non spatial memory improved at both durations, whereas spatial memory was improved after long-term treatment but not after short-term. Increased neurogenesis after 12-week treatment.
Belviranlı et al. (2013)	12 days	(1) Aged control group + vehicle; (2) Aged Cur group (300 mg/kg/day, p.o)	Female Wistar rats (N = 20; n = 10/group)	MWM	The effect of CUR on cognitive impairments and oxidative stress induced by age.	Administration of CUR significantly improved spatial learning and memory, whereas some markers of oxidative stress were decreased.
Yu et al. (2013)	21 days	(1) Young control group + vehicle; (2) Aged control group + vehicle; (3) Aged CUR group (50 mg/kg, i.p); (4) Aged CUR (50 mg/kg, i.p) + 7-NI (150 mg/kg, i.p); (5) Aged 7-NI (150 mg/kg, i.p)	Male Kunming mice (N = 48; n = 12/group)	NORT, PA	To investigate the effect of CUR on cognitive decline caused by aging and to explore its mechanism of action.	CUR alleviated memory impairment in aged mice.
Vidal et al. (2017)	60 days	(1) Aged control group + vehicle; (2) Aged CUR treated group (100 mg/kg/day, p.o)	Male Sprague-Dawley rats (N = 20; n = 20 per group)	NORT	To investigate the effects of curcumin treatment in aged rats and its relation with neurogenesis.	CUR improved memory and elevated dendritic spine density and length in certain brain regions.
Moore et al. (2017)	8 months	(1) Middle aged control group + vehicle; (2) Middle aged CUR treated group (500 mg in diet)	Male & female rhesus monkeys, *Macaca mulatta*, (N = 17; $n_1 = 9$, $n_2 = 8$)	DNMS, DRST	The effect of CUR on aging related memory deficits.	CUR improved spatial but not recognition memory in middle aged monkeys.

CUR = curcumin, i.p. = intraperitoneal, p.o. = per os (orally), i.g. = intragastrical, s.c. = subcutaneous injection, i.v. = intravenous, i.n. = intranasal, ICV = intracerebroventricular, WT = wild type, MWM = Morris Water Maze, PA = passive avoidance task, OFT = open field test, OLT = Object location test, ORT = object recognition test, NORT = Novel Object Recognition task, EPM = elevated plus maze, DNMS = delayed non-matching to sample task, DRST = delayed recognition span task, SAMP8 = senescence-accelerated mouse prone 8, SAMR1 = senescence-accelerated-resistant, qod = every alternate day, KI = knock-in, 3NP = 3-nitropropionic acid, C-SLN = curcumin solid lipid nanoparticle

promotes phosphorylation of tau protein was upregulated and neuronal loss was mitigated after treatment with curcumin.

More recently, Samy et al. (2016) studied the role of curcumin as well as erythropoietin in an ICV-STZ rat model. Animals were injected with saline or STZ. The latter group was treated subsequently with vehicle, curcumin (80 mg/kg/day, p.o), erythropoietin (500 IU/kg every other day, i.p) or with a combination of curcumin and erythropoietin for three months. Administration of curcumin and/or erythropoietin restored behavioral, histological and biochemical ICV-STZ induced alterations. However, curcumin was considered preferable due to its less severe long-term adverse effects compared to erythropoietin.

Contrary, a study evaluating prolonged administration of oral curcumin at doses of 25, 50 and 100 mg/kg, found no beneficial effect in short-term spatial memory of ICV-STZ infused rats (Bassani et al., 2017). However, an improvement was detected in short term recognition memory. Additionally, even though curcumin did not increase neurogenesis, a reduction of neuroinflammatory biomarkers was observed, which according to authors could possibly contribute to the frequently observed therapeutic effects of curcumin.

The familial form of AD (FAD) was studied by Zhang et al. (2015), who evaluated the protective effect of curcumin at 50, 100, and 200 mg/kg, i.p on intraventricularly injected $A\beta_{1\text{-}42}$ animals. Acute treatment with curcumin did not exert positive results. However, cognitive deficits, shown at the Y-maze and MWM, improved after chronic treatment (7-day administration) with 200 mg/kg curcumin compared to placebo. The results were comparable to the sham group. Similarly, Wang et al. (2013) and Yin et al. (2014) tested the effect of curcumin (300 mg/kg, i.p) on a $A\beta_{1\text{–}40}$ AD model and found that curcumin reversed spatial learning and memory impairments concomitantly promoting hippocampal regeneration.

Frautschy et al. (2001) tested whether dietary curcumin has a protective effect on Aβ-induced neurotoxicity when administered for 2 months prior to $A\beta_{1\text{-}42}$ and Aβ/HDL injection. A dose of 500 ppm of curcumin reversed spatial memory impairments as compared to the untreated Aβ-infused rats. Additionally, curcumin protected against Aβ deposits to a greater extent than ibuprofen. Another group evaluated curcumin (300 mg/kg, i.p) on a $A\beta_{1\text{-}40}$ model (Wang et al., 2011). Curcumin improved spatial memory to levels comparable to the sham group and suppressed neuronal apoptosis in the hippocampus by balancing the expression of the two apoptotic genes, Bax and Bcl-2.

The effect of different doses of curcumin was explored by Wang et al. (2014). This group utilized an APP/PS1 double transgenic AD model to examine the effect of low (160 ppm) and high (1000 ppm) dose of curcumin after administration for 6 months in diet. The researchers detected a significant cognitive improvement at both doses compared to the untreated group, while a significant dose-response effect was found throughout time with higher doses of curcumin producing greater cognitive improvement. In addition, data suggest that curcumin reduced Aβ deposits potentially by promoting autophagy.

3.1.1.2. Formulated curcumin. Despite the positive effects of curcumin on cognition, its main disadvantages when administered to a human organism are the low bioavailability, the rapid gastrointestinal metabolism and the poor blood brain barrier (BBB) penetration. Therefore, many formulations aiming to improve the bioavailability and stability of curcumin have been developed. One of these formulations includes polymersomes (POs) loaded with curcumin, accompanied by transferrin (Tf) and Tet-1 peptide (Tf/Tet-1-POs) (Jia et al., 2016). POs are artificial vesicles in which the drug is loaded to control permeability and increase stability. In addition, Tf is used to increase BBB permeability via endocytosis and Tet to facilitate the delivery to neurons due to its affinity with the ganglioside GT1B receptor on neurons. In the study by Jia et al. (2016), $A\beta_{1\text{-}42}$ AD mice were treated with curcumin (15 mg/kg, i.v) for 14 consecutive days to test different combinations of the abovementioned constituents. Results illustrated a significant improvement of Aβ-induced spatial and learning memory in mice treated with curcumin-Tf/Tet-1-PO and curcumin-Tf-PO compared with the untreated controls. The fact that animals treated with the empty Tf/Tet-1-PO did not display improvement in their performance suggests that curcumin is the compound contributing to the beneficial outcome.

Another formulation of curcumin was evaluated by Hoppe et al, who tested the differential effects of free curcumin and curcumin-loaded lipid-core nanocapsules (Cur-LNC) for 10 days in an $A\beta_{1\text{-}42}$-induced model (Hoppe et al., 2013). The results showed significant improvement in cognitive tests for both formulations of curcumin. Interestingly, a 20-fold lower dose of Cur-LNC (2.5 mg/kg/day, i.p) demonstrated similar neuroprotective effects as the high dose free curcumin (50 mg/kg/day). Furthermore, downregulated levels of the proinflammatory cytokines TNF-α and IL-1β in the hippocampus were observed only after administration of Cur-NLC, indicating higher biodistribution of curcumin under nanoparticle formulation.

Tiwari et al. (2013) reported comparable results. Curcumin-loaded biodegradable poly (lactic-*co*-glycolic acid) (PLGA) nanoparticles (Cur-PLGA-NPs) were found to be effective in reversing cognitive impairment and increasing neurogenesis in an AD rat model at a lower dose than uncoated natural curcumin after a three-week treatment. Specifically, after intraperitoneal injections at dosages of 10 and 20 mg/kg of Cur-PLGA-NPs, a 2.1- and 2.8-fold respective increase was reported in brain curcumin levels compared to the same doses of natural curcumin, indicating increased bioavailability of this formulation.

Ahmed et al. (2010) compared the effects of the parent curcuminoid mixture with its three separate constituents, specifically curcumin, bisdemethoxycurcumin and demethoxycurcumin in Aβ-infused rats. All components showed a memory-enhancing effect at 3 mg/kg, i.p, whereas the curcuminoid mixture had no effect on memory at the same dose. At 30 mg/kg, i.p all treated groups showed a significant beneficial effect on memory, but the three separate components showed additional improvement over time, suggesting that the parent curcuminoid mixture might not be as effective as its separate components. On a molecular level, after short term treatment the curcuminoid mixture and the bisdemethoxycurcumin improved post-synaptic density protein (PSD-95) in the hippocampus, a marker of postsynaptic plasticity, with the lower dose (3 mg/kg) being more effective. However, after prolonged administration the other two components show similar outcome. Interestingly, after long term treatment a high dose of demethoxycurcumin (30 mg/kg) seemed to be more effective in augmenting synaptophysin and calcium/calmodulin dependent protein kinase type IV (camkIV) expression - biomarkers of synaptic plasticity - compared to the other compounds. The authors suggested that these results probably indicate that different compound compositions could result in different beneficial outcomes depending on the model or the type of the disease.

Yanagisawa et al. (2015) utilized the double transgenic APP/PS1 model to compare three forms of dietary curcumin; natural curcumin, FMeC1 and FMeC2. FMeC1 is a derivative of curcumin substituted at the C-4 position, which previously has shown to bind to Aβ deposits, while leaving Aβ monomers untouched (Yanagisawa et al., 2010). FMeC2 is a product of FMeC1 hydrolysis. Improved spatial memory comparable to the sham group, was evident in the group treated with FMeC1; however, no memory improvement was observed in the group treated with free curcumin or FMeC2. Likewise, treatment with FMeC1 reduced the accruement of $A\beta_{40}$ and $A\beta_{42}$, while this trend was not observed after treatment with natural curcumin or FMeC2. Additionally, Okuda et al. (2017) evaluated a new derivative of curcumin, called PE859 (1 and 3 mg/kg/day, i.g), on a SAMP8/TaSlc mouse strain. No significant differences were displayed on spatial learning and memory. However, PE859 seemed to diminish insoluble $A\beta_{1\text{-}40}$ but not $A\beta_{1\text{-}42}$ deposits.

Besides Aβ deposits NFT's accumulation is a hallmark of AD. For that reason, Ma et al. (2013) explored the effect of dietary solid lipid

nanoparticle *Longvida*® (500 ppm) on a Tau mice model with intraventricular injections of tau dimers. Their findings suggest that curcumin supplementation may improve memory and result in a number of biochemical alternations leading to suppressed tau aggregation. To examine abnormal deposition of both Aβ and NFT's, Sundaram et al. (2017) chose to use a p25 transgenic mice model to evaluate the same dietary form of curcumin. Both features of AD were reduced presumably due to suppressed levels neuroinflammatory cytokines MIP-1α, TNF-α and IL-1β. Additionally, *Longvida*® improved spatial and working memory as observed in the 8-arm radial maze.

More recently, McClure and his team (2017) introduced an inhaled formulation of curcumin to increase BBB permeability and tested its efficacy in preventing AD. They have shown that treating young 5XFAD mice with intranasal curcumin prevented memory deficits and Aβ plaque burden in adulthood as compared to the untreated mice. In addition, no side effects or incidents of toxicity were reported in the respiratory and the circulatory system of the animals as expected to due to the nebulized form of curcumin.

Overall, the vast majority of AD animal models indicates that curcumin has both preventive and therapeutic effects on cognition. Beneficial effects are observed not only on molecular but also on behavioral level. Formulated curcumin seems to result in increased bioavailability compared to the natural compound.

3.1.2. Non-pathological ageing

Aging is a physiological process associated with functional, morphological and biochemical alternations in the central and peripheral nervous system. The biological underpinnings of aging remain unclear; however, oxidative stress, inflammation and mitochondrial dysfunction have been suggested to play an important role in age-related cognitive impairments, causing individuals to become vulnerable for developing neurodegenerative diseases (Troen, 2003). Given its potential positive effects on oxidative stress and inflammation, curcumin could be of interest in ameliorating aging-associated cognitive impairments and/or reducing the risk for development of neurodegenerative diseases, such as AD.

Kumar et al. (2011) studied the neuroprotective effects of orally administered curcumin at 15 and 30 mg/kg using galantamine (5 mg/kg) -an acetylcholinesterase inhibitor prescribed for the treatment of cognitive decline in AD- as a positive control group in a D-galactose (D-gal) animal model. D-gal is a decreasing sugar that can accelerate senescence and induce cognitive dysfunction to experimental animals in a way that resembles human aging. Groups treated either with curcumin or galantamine performed better on cognitive tasks compared to the untreated D-gal group, even though locomotor activity remained the same in all groups. In addition, both curcumin and galantamine diminished levels of oxidative stress and mitochondrial dysfunction. The results thus indicate that CUR could be an alternative treatment for aging-induced cognitive deficits with a higher dose showing more beneficial results.

Equally, Nam et al. (2014) studied the effects of orally administered curcumin at 300 mg/kg in D-gal induced mice. A beneficial trend of curcumin on learning and spatial memory was observed in D-gal mice treated with curcumin as compared to the vehicle treated D-gal mice. No significant difference was found in cognitive performance between curcumin and vehicle treated healthy animals. Results demonstrated increased neuronal proliferation in the hippocampus after administration of curcumin, as evident by the elevated brain-derived neurotrophic factor (BDNF) protein expression and increased phosphorylation of the transcription factor CREB in the respective brain region.

The same model was applied to compare the synergistic effect of curcumin and piperine versus curcumin and piperine monotherapy when administered orally at doses of 20 mg/kg or 40 mg/kg for curcumin and 6 mg/kg or 12 mg/kg for piperine by the group of Banji et al. (2013a,b). Combined curcumin and piperine showed superiority, in a dose dependent manner, compared to separate administration in ameliorating memory and normalizing oxidative burden, biochemical levels and hippocampal morphology. Moreover, using a similar study design they compared the same compound synergism but this time using higher doses of piperine (Banji et al., 2013a,b). As in the previous study, co-administration of curcumin and piperine ameliorated movement and cognitive deficits caused by D-gal administration, while also reducing oxidative stress in a dose dependent manner. One year later the same group evaluated the effects of combined curcumin and hesperidin (glycoside). Likewise, both separate and co-administration augmented behavioral performance with higher doses of the mixture demonstrating better overall profile in reducing mitochondrial and oxidative damage as well as apoptosis (Banji et al., 2014).

Sun et al. (2013) studied the effects of 20 and 50 mg/kg curcumin when administered intragastrically using senescence-accelerated mouse prone 8 (SAMP8 mice). SAMP8 is a line that closely mimics human's phenotype of senescence; therefore, it was compared with a normal aging SAMR1 strain. They found an improvement in spatial memory at both doses of curcumin compared to the untreated SAMP8 mice as well as enhanced antioxidant capacity and synaptic plasticity. Again, stronger effects were found on the high dose of curcumin (50 mg/kg).

A different approach was followed by Dong et al., who instead of modeling senescence in young animals, evaluated the effect of curcumin in normal aging rats (Dong et al., 2012). Non-spatial and spatial memory were tested after 6 and 12 weeks of curcumin treatment (480 mg/kg in chow). After 12-weeks curcumin treatment, spatial memory significantly improved in the aged rats, whereas no effect was found after a 6-week administration. A subtle improvement in non-spatial memory was detected in the curcumin group after both treatment durations. Interestingly, increased neurogenesis was observed in the hippocampus of the rats after prolonged administration of curcumin.

Another study found small beneficial effects of curcumin (300 mg/kg/day, p.o) in aged rats (Belviranlı et al., 2013). Performance on learning and spatial memory improved in curcumin treated compared to vehicle treated rats. However, except from a downregulated marker of oxidative stress (malondialdeyde) in the group treated with curcumin the other markers remain unchanged (protein carbonyl and glutathione). Yu et al. also examined the effect of prolonged administration of curcumin on aged rats (Yu et al., 2013). Curcumin ameliorated cognitive deficits induced by aging. The underlying mechanism of curcumin's action could be attributed to the activation of the neuronal nitric oxide synthase/nitric oxide (nNOS/NO) pathway.

In a more recent study, Vidal et al. (2017) similarly examined the effect of oral curcumin on aged rodents. Animals treated with curcumin exhibited better performance on recognition memory as compared to the vehicle treated group. Additionally, curcumin improved dendritic spike density and dendritic length in the hippocampus and the prefrontal cortex, however, with regards to the amygdala the results were not consistent across measurements.

The only study examining non-human primates was the study of Moore et al. (2017). In this study middle aged rhesus monkeys received curcumin or placebo in their diet to assess its effect on age related cognitive deficits. Results revealed amelioration of spatial memory in the curcumin treated animals, however, no improvement was observed concerning the visual recognition memory. According to the authors, this deviation could probably be explained by the fact that in middle aged monkeys recognition memory has not begun to decline yet, whereas spatial memory is typically deteriorated at this age-range.

In general, results indicate that curcumin may benefit age-related cognitive impairments. Higher doses of curcumin seem to be more effective compared to the lower doses regardless the route of administration and co-administration with piperine seems to enhance further curcumin's effect.

Table 2
Summary of the included human studies.

Study	Study Design	Study design & Dose	Duration	Disorder Age (N)	Cognitive Measurements	Primary Objective	Main results	AE
Rainey-Smith et al. (2016)	R, DB, PC, PG	(1) Placebo (2) 1500 mg/day BiocurcumaxTM	12 months	Healthy elderly 40–90 y (N = 96; n1 = 57, n2 = 39)	(1) RAVLT (2) COWAT; (3) WAIS-R; (4) Computerised CogState battery; (5) MoCA	Ability of curcumin to prevent cognitive decline	Cognitive decline after 6 months in placebo but not in curcumin. Effect on mood	23 gastrointestinal complains (2 on placebo)
Cox et al. (2015)	R, DB, PC, PG	(1) Placebo; (2) 400 mg Longvida® (assessment: 1 and 3 h and 4-week treatment)	4 weeks	Healthy elderly 60–85 y (N = 60; n_1 = 30, n_2 = 30)	(1) COMPASS; (2) DASS21; (3) CFS; (4) BL-VAS; (5) STAI	Effect of acute and chronic administration of curcumin on cognition, mood and biochemical. measures	Single-dose improved performance on working memory and sustained attention. Four-week treatment improved WM and reduced fatigue. Downregulation in total and LDL cholesterol.	NO
Baum et al. (2008)	R, DB, PC, PG	(1) Placebo; (2) CUR (1 g); (3) CUR (4 g) → CUR was given either as powder or in capsules	6 months	Cognitive decline/ possible AD > 50 (N = 27; n_1 = 8, n_2 = 8, n_3 = 11)	MMSE	Safety, biochemical and cognitive changes in AD	No differences on cognitive decline were observed. Similar bioavailability between 1 and 4 g CUR, but better bioavailability when CUR administered in capsules	4 gastrointestinal (2 on placebo, 2 on 1 g, 1 on 4 g), 3 respiratory tract infections (2 on placebo, 1 on 1 g), 3 dizziness (1 on placebo, 1 on 1 g, 1 on 4 g), 2 delusions (1 on 1 g, 1 on 4 g), 2 edema (1 on placebo, 1 on 1 g), 1 hearing impairment (on placebo)
Ringman et al., (2012)	R, DB, PC, PG (Open label extension)	(1) Placebo; (2) Curcumin C3 Complex ® (2 g/day); (3) Curcumin C3 Complex ® (4 g/day)	24 weeks (48 weeks- open label extension)	Mild-to-moderate AD > 49 (N = 30; n_1 = 10, n_2 = 10, n_3 = 10)	(1) (ADAS-Cog); (2) NPI; (3) ADCS-ADL	Safety and tolerability of Curcumin C3 Complex ®. Efficacy in cognition	Non-significant change on MMSE results after Curcumin C3 Complex ® administration. Low bioavailability of the compound and no alternations of AD biomarkers	Three gastrointestinal symptoms
Small et al., (2018)	R, DB, PC, PG	(1) Placebo; (2) Theracurmin® (90 mg CUR) orally, b.i.d	18 months	Non-demented 51–84 y (N = 40; n_1 = 19, n_2 = 21)	(1) SRT; (2) BVMT-R; (3) Trail Making Test	The effect of curcumin on memory performance and on deposition of amyloid plaques and tau tangles	Theracurmin® improved memory and attention performance and prevented neuropathological deposition in amygdala and hypothalamus	Gastrointestinal complain (4 in the curcumin and 2 in the placebo group)

R = randomized, DB = double blind, PC = placebo control, PG = parallel groups, WM = working memory, RAVLT = Rey Auditory Verbal Learning Test, COWAT = Controlled Oral Word Association Test, WAIS-R = Wechsler Digit Symbol Scale from the Wechsler Adult Intelligence Scale revised, MoCA = Montreal cognitive assessment, COMPASS = Computerized Mental Performance Assessment System, DASS21 = 21-item version of the Depression, Anxiety and Stress Scales, CSF = Chalder Fatigue Scale, BL- VAS = Bond-Lader Visual Analogue Scales, STAI = State-Trait Anxiety Inventory, MMSE = Mini- Mental State Examination, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, NPI = Neuropsychiatric Inventory, ADCS-ADL = Alzheimer's Disease Cooperative Study - Activities of Daily Living, NPI-Q = Neuropsychiatric inventory-brief questionnaire, b.i.d = bis in die, SRT = Buschke Selective Reminding Test, BVMT-R = Brief Visual Memory Test-Revised.

3.2. Clinical trials

With regards to human data, a few randomized clinical trials (RCTs) have been conducted measuring cognitive functioning after curcuminoid administration. The majority of these trials included an elderly population, with or without AD. In total five articles met the inclusion criteria. Study specifics are displayed in Table 2.

Rainey-Smith et al. (2016) conducted a randomized study in which participants between 40 and 90 years old without cognitive impairment were tested on a battery of clinical and cognitive testing after 12 months of 1500 mg *Biocurcumax*™ or placebo administration. The results showed cognitive decline after 6 months in the placebo group on the Montreal cognitive assessment, that is used to assess general cognitive functioning; however, cognitive performance in the curcumin group remained stable. This difference on Montreal cognitive assessment was not observed after the 12-month follow-up. Other cognitive and clinical measures revealed no differences between groups across time. The authors concluded that curcumin does not enhance cognition, but rather attenuates its decline over time. It must be noted that out of 160 participants that underwent baseline assessment, 23 subjects, two of which belonged in the placebo group, were excluded from the analysis due to reported gastrointestinal complains, suggesting that the high dose of *Biocurcumax*™ used in the study has probably impacted tolerability of the compound.

A comparable population was assessed by Cox et al. (2015). Sixty healthy adults, between 65 and 80 years of age, were tested using an acute (1 and 3 h after a single dose), chronic (four weeks) and acute-on-chronic (1 and 3 h after single dose following 4-week treatment) administration of 400 mg dose of *Longvida*® Optimized Curcumin. This compound is a solid lipid formulation that contains approximately 80 mg of curcumin. One-hour post-dose, curcumin administration had a beneficial effect on working memory and sustained attention measurements. A similar pattern was observed after chronic administration; however, no significant results were found 3 h post-acute administration. Moreover, mood was improved; increased calmness and a reduction in fatigue were observed in the chronic curcumin group.

Examining the effect of curcumin on cognition, Baum et al. (2008) conducted a pilot trial in a Chinese adult population, over 50 years of age with progressive cognitive impairment (probable or possible AD). Curcumin was administered at 1 or 4 g either in capsules or as powder for 6 months and was compared to placebo. No differences in Mini-Mental state examination (MMSE) scores were detected throughout time or among treatments. Additionally, there was no significant difference in serum $A\beta_{1\text{-}40}$ levels among treatments, however $A\beta_{1\text{-}40}$ levels tended to increase on curcumin, indicating reduced Aβ aggregation in the brain after treatment with curcumin. Additionally, curcumin increased vitamin E, reflecting a potential antioxidant activity. Interestingly, capsules exhibited better bioavailability compared to the powder formulation, whereas no differences in curcumin's metabolites was observed between 1 and 4 g. Furthermore, no severe side effects were reported after curcumin's administration.

Ringman et al. (2012) evaluated the efficacy of a different curcumin formulation; the Curcumin 3 Complex®, which is the parent curcuminoid mixture comprising the three different constituents (curcumin, bisdemethoxycurcumin and demethoxycurcumin). The compound was administered for 24 weeks in a population with mild to moderate AD. Participants were randomized into 3 groups (placebo, 2 g/day and 4 g/day curcumin). The experiment extended for 24 weeks, during which the placebo group was randomly divided into the 2 or 4 g/day groups. No evidence of Curcumin C3 Complex® efficacy at cognition or at Aβ and tau levels in plasma and CSF were found, while low bioavailability in plasma was reported. Moreover, three participants of the curcumin group dropped out due to gastrointestinal complains.

More recently, Small et al. (2018) evaluated the effect of Theracurmin®, a compound that contains 90 mg of curcumin. Forty non-demented adults between 51 and 84 years of age were randomized to either Theracurmin® or placebo twice a day for 18 months. Visual and verbal, short-term memory as well as attention improved in the Theracurmin® group in comparison to the placebo group. Additionally, data derived from FDDNP-PET scans indicate reduction in amyloid and tau accumulation in the amygdala and stable levels in the hypothalamus of the curcumin treated group compared to respective elevated levels in the placebo group.

Results of human studies are mixed with regards to curcumin's use on cognitive impairments. Besides *Biocurcumax*™ that was administered in a high dose, the other compounds have demonstrated a safe profile. Due to the limited number of published RCTs, the findings remain inconclusive.

4. Discussion

Curcumin's diverse array of molecular targets, that offers anti-inflammatory and antioxidant properties, have made it an interesting compound for the enhancement of cognitive function. Therefore, the aim of the current review was to provide an overview of both preclinical and clinical studies examining the effectiveness of curcumin for cognitive enhancement both in Alzheimer's disease and healthy aging.

4.1. Summary of findings

4.1.1. Pre-clinical studies

Preclinical models have predominately demonstrated a positive effect of curcumin on cognitive functioning. Common practice in animal research is the inclusion of two control groups; a sham group that undergoes the same operational procedures as the experimental group without the induction of cognitive and biochemical alternations, and/or a control group with induced cognitive impairments treated with vehicle. Some preclinical studies have reported improvement of the curcumin treated group in cognitive testing comparable to the sham group, suggesting complete recovery of cognitive functions (Wang et al., 2011; Yanagisawa et al., 2015; Zhang et al., 2015). However, the majority of studies have reported superiority of curcumin compared to the control group. Interestingly, in healthy or sham animal groups treated with curcumin cognitive performance was not altered (Ishrat et al., 2009; Nam et al., 2014). This suggests that curcumin is able to reverse or prevent disease induced cognitive decline rather than enhance further 'normal' cognitive functioning. This is probably related to the ability of curcumin to act directly on Aβ plaques as well as to its anti-inflammatory and antioxidant properties.

Indeed, a number of preclinical studies have reported down-regulation of biomarkers of inflammation (e.g. TNF-α, IL-1β) and oxidative stress (e.g. lipid peroxidation, ROS, nitrite and glutathione) believed to be involved in cognitive impairments, confirming the anti-inflammatory and antioxidant properties of curcumin (Agrawal et al., 2010; Banji et al., 2013a,b; Banji et al., 2014; Bassani et al., 2017; Hoppe et al., 2013; Ishrat et al., 2009; Kumar et al., 2011; Sandhir et al., 2014; Singh & Kumar, 2017; Sundaram et al., 2017). Increased neurogenesis observed after treatment with curcumin or initiation of autophagy suggest other possible actions of this compound in potentiating cognition (Dong et al., 2012; Nam et al., 2014; Tiwari et al., 2013; Wang et al., 2013a,b, 2014). These outcomes highlight the wide array of molecular mechanisms of curcumin compared to the existing mechanistic target cognitive enhancers.

4.1.2. Clinical studies

Contrary to animal studies, only a limited number of clinical studies has examined curcumin's effect on human cognitive functioning. The results of these studies are inconsistent; some studies report no cognitive enhancing effects of curcumin (Baum et al., 2008; Ringman et al., 2012) whereas other studies suggest a beneficial effect of curcumin on cognition (Cox et al., 2015; Rainey-Smith et al., 2016; Small et al., 2018). Similar to animal research some studies suggest protective

mechanisms of curcumin against cognitive decline (Baum et al., 2008; Small et al., 2018). Findings concerning Aβ reduction are ambiguous, since most of the peripheral measurements, such as plasma, serum and CSF levels have not detected significant changes in Aβ or tau levels between curcumin and placebo (Baum et al., 2008; Ringman et al., 2012); however, neuroimaging supports that curcumin reduces Aβ deposits in the brain (Small et al., 2018). Unfortunately, only one study has reported measurements on oxidative stress biomarkers (Baum et al., 2008), while none of the studies have reported measurements on inflammatory biomarkers, although these are the main targets of curcumin and have shown great improvement in animal research.

4.2. Translational and methodological limitations

Results of animal and human studies are not completely aligned. In animal research, curcumin predominantly yields promising outcomes for the treatment of cognitive functions in AD and aging, which is not observed in all human trials and is possibly related to the different types of memory studied in animals and humans. Preclinical research has mainly evaluated spatial working memory and learning. Nevertheless, in patients suffering from AD episodic and working memory are the first to be affected at the onset of the disease (Gold & Budson, 2008; Jahn, 2013). Perhaps the use of tests measuring episodic memory along with the standard measurements of spatial working memory could increase the translational value of the animal studies; however the reliability of those tests is still debatable (Griffiths & Clayton, 2001; Roberts, 2006). In addition, this difference in types of impaired memory between humans and animals poses the question of whether underlying biological differences might lead to impairment of different aspects of memory across species.

It is known that none of the animal models authentically reproduces the full constellation of symptoms observed in human pathology (Jackson-Lewis et al, 2012; LaFerla & Green, 2012). In both cases, a wide variety of models has been utilized to reproduce the separate disease-like symptoms. However, different models affect different aspects of disease-related mechanism and pathology. For instance, in AD some animal models do not develop NFTs, some models develop Aβ-40 while others Aβ-42 accumulation. The same applies to non-pathological aging. In addition, even though the existing animal models are valuable for revealing key inflammatory or oxidative biomarkers involved in downstream pathologies of both conditions, none of these models reproduces the exact inflammatory or oxidative response due to differences in the nature of inflammation/oxidative stress between humans and rodents (LaFerla & Green, 2012).

An important issue, that could contribute to the difference in results between animals and human studies, is the heterogeneous methodology used in preclinical and clinical studies. For example, in preclinical studies different formulations of curcumin in different strains were used as well as different doses in different routes of administration e.g. orally, intraperitoneal, intravenously, etc. In addition, the use of different behavioral tests that evaluated different aspects of memory and learning affects generalizability of results, especially considering that in some cases distinction between motor and cognitive components may be difficult (Sterniczuket al., 2010). All these factors complicate a reliable transition from preclinical to clinical studies.

Furthermore, similar to animal studies, different formulations and different doses of curcumin were used in human studies. Also, different tests were used to assess cognitive performance. The majority of studies included a relatively small number of participants resulting in limited power (Baum et al., 2008; Ringman et al., 2012; Small et al., 2018). Additionally, the differences in ethnicity, namely Caucasian and Asian, further complicates interpretation of the different results, since certain drugs can differently affect people according to their race/ethnicity (Burroughs et al., 2002). For instance, genetic factors, such as polymorphisms or cultural differences, e.g. increased use of curcumin in many Asian cuisines, can be major determinants of curcumin's effects. So far, none of the studies have reached Phase III in clinical trials, suggesting that curcumin has not fully met expectations. However, for reasons outlined above and because of the restricted number of clinical studies performed to date, it is not possible to directly compare clinical studies and draw concrete conclusions about the effectiveness of curcumin yet.

4.3. Future directions

The major drawback of curcumin supplementation for therapeutic purposes is the low bioavailability of the compound. Many equivalents of curcumin have been developed to improve this. As mentioned previously, administration of any of the three constituents (curcumin, bisdemethoxycurcumin and demethoxycurcumin) separately instead of the parent curcuminoid mixture was recommended as a more efficient way of treatment (Ahmed et al., 2010). Furthermore, a synergistic effect of curcumin with other dietary supplements, such as piperine, α-lipoic acid, N-acetylcysteine, B vitamins, vitamin C, and folate, has been suggested to enhance its effects (Parachikova, et al., 2010; Rinwa & Kumar, 2012). However, at present nanoparticles are mainly used, since they demonstrate better BBB penetration and provoke deeper biochemical changes than free curcumin (Hoppe et al., 2013; Kundu et al., 2016; Ma et al., 2013; Sandhir et al., 2014; Tiwari et al., 2013). Nevertheless, there is still room for improvement and future research should focus on ways to further increase curcumin's systemic bioavailability, in particular by improving BBB permeability and reducing first pass metabolism of the compound.

A dose-response relationship should also be taken into account. The optimal dose would have maximum cognitive enhancing effects with the safest pharmacokinetic profile. It is important to mention that the vast majority of animal studies illustrates beneficial effects of curcumin on cognition in a dose dependent manner with the higher dosages generally being more effective compared to lower dosages used in animals (Reeta et al., 2009; Sun et al., 2013; Tiwari et al., 2013; Tiwari & Chopra, 2013; Wang et al., 2014; Zhang et al., 2015). However, there are animal studies that report an inverted U-shape effect in Aβ plaques reduction but behavioral data are not available (Lim et al., 2001). At the same time, human studies suggest a ceiling effect concerning the dose of curcumin (Baum et al., 2008). Subsequently, a medium dose range might be preferable at clinical settings. The existing studies have evaluated disperse formulations of curcumin impeding any comparison between compounds. Therefore, it is of substantial importance to conduct reliable pharmacokinetic/ pharmacodynamics (PK/PD) and comparative studies in order to determine a standard dose using the analogue that would be able to reach brain targets in the most efficacious way.

An interesting subject for future research would be the impact of nutritional status on curcumin's therapeutic effects. Curcumin is a highly lipophilic molecule. One animal study showed aggravated cognitive performance in rats consuming high-fat diet in conjunction with curcumin administration (Wu et al., 2006). In contrast, clinical studies suggest that consuming a meal rich in fat prior to curcumin's administration slows down gastric elimination and allows maximum absorption of the compound (Lao et al., 2006; Ringman et al., 2012; Vareed et al., 2008). Nevertheless, a number of pharmacokinetic clinical studies has been performed in fasted subjects (Bertolino et al., 1998; Gota et al., 2010; Kanai et al., 2012; Kocher et al., 2015). The clinical trials discussed here used different dietary patterns prior administration of curcumin.

Another issue for future consideration is the targeted population in human studies. Clinical studies have mainly used participants without established cognitive dysfunction. However, in preclinical studies, amelioration of cognitive deficits was evident in cognitive impaired rodents. Curcumin did not exert beneficial effects on cognition of healthy or sham control animals, suggesting that curcumin enhances cognitive deficits rather than boosts normal cognitive functioning

(Ishrat et al., 2009; Nam et al., 2014). Clinical findings have also supported that this compound does not significantly improve cognitive functioning in healthy or mildly cognitive impaired population, but probably prevents or stabilizes cognitive decline (Cox et al., 2015; Rainey-Smith et al., 2016; Ringman et al., 2012; Small et al., 2018). Therefore, evaluation of patients with established cognitive deficits might yield different results.

Lastly, an important factor that could benefit future trials, is an extended duration of treatment. Curcumin exerts its therapeutic effect through anti-inflammatory and antioxidant pathways. However, regulation of inflammation, oxidative stress or neurogenesis are lengthy processes. In human trials, the maximum duration of curcumin's administration was 18 months and yielded the most positive results compared to the rest of the studies that lasted one year or less (Small et al., 2018). Considering the low bioavailability of the compound, prolonged periods of treatment may be required to detect essential improvement in cognition.

4.4. Conclusion

In conclusion, numerous preclinical studies have demonstrated beneficial effects of curcumin on cognition in AD and non-pathological aging. However, a limited number of human studies was identified, and these results are less consistent than results of preclinical work. Preliminary evidence from human studies supports preclinical findings that curcumin may stabilizes/prevents cognitive decline rather than improves it in healthy population. Since, curcumin is an interesting compound with potential capability of preventing cognitive decline, it is crucial to find ways to bridge this translational gap. An important advantage of curcumin is that constitutes a natural, widely available compound. Thus, it does not involve a great economic burden for the patients that might benefit from its use. Additionally, even though studies have reported mild side effects in the elderly patients at a high dose, curcumin demonstrates a safer profile compared to the current compounds. Thus, as current treatments for cognitive impairments remain insufficient and are accompanied by severe side-effects, curcumin may be a promising alternative. However, further research to improve curcumin's bioavailability is crucial and more human trials examining curcumin's cognitive enhancing effect are necessary.

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