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Review

Targeting cognitive aging with curcumin supplementation: A systematic review and meta-analysis

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ABSTRACT

Background: Cognitive aging is a growing public health concern, and curcumin, a bioactive compound derived from turmeric, has been proposed as a potential intervention to support cognitive function due to its anti-inflammatory and antioxidant properties.

Objectives: This systematic review and meta-analysis aimed to evaluate the effects of curcumin on cognitive outcomes related to aging.

Methods: A comprehensive search of PubMed, Embase, Cochrane Library, Web of Science, and Scopus was conducted to identify studies published up to June 18, 2024, including both in vivo preclinical animal studies and randomized controlled trials (RCTs) assessing curcumin's effects on cognitive function. In vivo animal studies using Alzheimer's disease (AD) models and RCTs in human participants were included. Data were extracted and analyzed using meta-analytic techniques.

Results: In preclinical in vivo murine studies (n = 25; total animals = 572), curcumin consistently improved both acquisition memory (SMD = -1.78, 95 % CI: -2.12 to -1.43) and retention memory (SMD = 2.36, 95 % CI: 1.72 to 3.00) in rodent models of AD. Ten human studies include 531 participants. Overall, curcumin showed no significant effect on global cognitive outcomes compared to placebo (SMD = 0.14, 95 % CI: -0.78 to 1.07). Subgroup analyses revealed significant improvements in working memory (SMD = 1.01, 95 % CI: 0.15 to 1.87) and processing speed (SMD = 0.37, 95 % CI: 0.07 to 0.67). The incidence of adverse events was higher in the curcumin group than in the control group.

Conclusions: Preclinical in vivo evidence suggests curcumin enhances cognitive function in AD models. However, human studies show inconsistent findings with benefits limited to specific cognitive domains. Larger, well-designed randomized controlled trials are needed to establish curcumin's efficacy and safety in cognitive aging.

1. Introduction

Curcumin is a natural polyphenolic compound derived from the rhizome of Curcuma longa (turmeric), widely studied for its anti-inflammatory, antioxidant, and neuroprotective properties [1–4]. Curcumin has demonstrated the potential to improve cognitive performance in preclinical in vivo animal models of Alzheimer's disease. Studies have shown that curcumin administration reduces amyloid-beta (Aβ) deposition, tau phosphorylation, and neuroinflammation in rodents, leading to significant cognitive improvements in memory and learning tasks [5–7].

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Furthermore, curcumin has been shown to enhance synaptic plasticity and promote neurogenesis in the hippocampus, a brain region critical for memory processing, potentially via upregulation of brain-derived neurotrophic factor (BDNF) [8]. In addition, curcumin exerts antioxidative effects by scavenging reactive oxygen species (ROS) and modulating inflammatory signaling pathways such as NF-κB [9,10]. Its ability to reduce pro-inflammatory cytokines, including IL-6 and TNF-α, further supports its therapeutic potential [3,11].

Clinical evidence supporting the effectiveness of curcumin in human cognitive aging is still evolving. Three observational studies have suggested that regular consumption of curcumin-rich curry may be associated with better cognitive performance and longer life expectancy in older adults [12–14]. These were not included in the meta-analysis due to their non-interventional design. Some randomized controlled trials (RCTs) have reported significant cognitive improvements in individuals with mild cognitive impairment (MCI) or early-stage Alzheimer's disease (AD) following curcumin supplementation, particularly in tasks assessing memory and executive function [15,16]. Curcumin supplementation has also been associated with reductions in neuroinflammatory biomarkers such as C-reactive protein (CRP) and IL-6 [16].

Despite these challenges, the compelling results from in vivo preclinical studies (hereafter referred to as preclinical studies) provide a strong rationale for evaluating curcumin's role in cognitive aging more systematically. This study aims to assess the effects of curcumin supplementation on cognitive outcomes related to aging through a systematic review and meta-analysis, integrating evidence from both in vivo animal models and human clinical trials. The goal is to clarify curcumin's therapeutic potential and inform future clinical applications in the prevention or delay of cognitive decline.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The review protocol was registered in the PROSPERO database (Registration ID: CRD42024563654).

2.1. Search strategy

2.1.1. Preclinical studies

The search, conducted from inception to June 18, 2024, employed the same databases and a tailored strategy incorporating MeSH terms and free-text keywords related to curcumin, cognition, and animal models. Reference lists of included preclinical studies were also screened for further relevant articles.

2.1.2. Human studies

A literature search was performed to identify randomized controlled trials (RCTs) evaluating the effects of curcumin on cognitive aging in humans. The search covered five electronic databases: PubMed, Embase, Cochrane Library, Web of Science, and Scopus, from inception to June 18, 2024. A combination of Medical Subject Headings (MeSH) terms and free-text keywords related to curcumin, cognitive aging, and humans were used. To enhance the inclusivity of the search, a "snowballing" approach was applied by screening reference lists of included studies for additional relevant articles.

The detailed search strategy for both preclinical and human studies is provided in Supplementary 1.

2.2. Selection criteria

Studies were included based on the following criteria: (1) Study types: RCTs. (2) Population: For preclinical studies, only rodent models of AD were included. For human studies, participants aged ≥ 18 years. (3) Intervention(s): Studies using curcumin or its extracts were included. For in vivo animal studies, no restrictions were applied regarding dosage form, dose, frequency, treatment duration, or administration route. For human studies, only curcumin administered in supplemental forms (e.g., capsules, tablets) was eligible, with no restrictions on dosage or administration parameters. (4) Outcome measures: For preclinical studies, any assessment type cognitive function; For human studies, cognitive outcomes were assessed using validated tests, such as MMSE, MoCA, and other standardized neuropsychological tests. Secondary outcomes included adverse events (e.g., nausea, dizziness). The incidence and severity of adverse events were analyzed.

Exclusion criteria included: (1) Publication type: review, conference abstracts, book chapters, commentary, or protocol. (2) Interventions: Curcumin is used in combination with other interventions (e.g., medications, supplements, or other treatments). (3) Others: Duplicate publications or studies with insufficient data for analysis, or studies assessing curcumin intake through dietary questionnaires or self-reported turmeric consumption without a defined intervention. (4) Language: Non-English publications.

2.3. Study selection

The study selection process was supported by EndNote, a reference management software, which was used to remove duplicates. Titles and abstracts were then screened manually against the predefined inclusion and exclusion criteria, followed by full-text review for eligible studies. Two independent reviewers (LY and NL) conducted all screenings, resolving disagreements through discussion or consultation with a third reviewer (LF).

2.4. Data extraction

Data were extracted into a pre-specified database by two independent reviewers (LY and NL) using a standardized extraction form, with discrepancies resolved by a third reviewer (LF). Extracted data included:

General information: author, publication year, country, study design, and sample size.

Participant characteristics (human studies): age, gender, and health status.

Animal model details (preclinical studies): species, strain, age, gender, and AD induction method.

Intervention details: dosage, dosing interval, administration route, control, and duration.

Outcome measures: cognitive test types, baseline and post-intervention scores, and adverse events.

Results: mean differences or effect sizes, confidence intervals, p-values, and variability measures.

2.5. Risk of bias assessment

Preclinical studies were evaluated using SYRCLE's Risk of Bias tool [18], with classifications of low, unclear, or high risk. Human RCTs were assessed using the Revised Cochrane Risk-of-Bias 2 tool (RoB 2) [19], classifying studies as low, some concerns, or high risk of bias. Assessments were conducted independently by LY and NL, with discrepancies resolved by LF.

2.6. Statistical analyses

Meta-analysis was conducted using STATA (version 16.1, Stata Corp LLC, College Station, TX). For continuous outcomes, standardized mean differences (SMD) with 95 % confidence intervals (CIs) were calculated to accommodate variations in measurement scales. For dichotomous outcomes, a risk ratio (RR) with 95 % CIs was computed. Data trans-

formations were applied when necessary to ensure consistency in effect size measures. Statistical significance was set at $p < 0.05$.

Heterogeneity was assessed using the I^2 statistic. fixed-effects model was applied if $p > 0.05$ and $I^2 \langle$ 50 %. A random-effects model was used if $p < 0.05$ or $I^2 \rangle$ 50 % [20].

Subgroup analyses explored potential heterogeneity sources based on predefined variables. Predefined subgroup analyses were performed separately for human and preclinical studies to investigate potential variations in cognitive outcomes. Human studies: Subgroups were categorized based on clinical diagnosis, with one group comprising AD patients and the other consisting of cognitively healthy older adults. Preclinical studies: Subgroups were based on species, strain, gender, model type, and delivery route to examine how these factors influenced cognitive function across various animal models of AD.

Sensitivity analyses evaluated robustness by excluding high-risk studies or outliers. Publication bias was assessed through funnel plots and Egger's test, with asymmetry and $p < 0.05$ indicating potential bias.

Publication bias was evaluated using funnel plot asymmetry and Egger's regression test for small-study effects [21]. Asymmetry and $p < 0.05$ suggested potential publication bias. All statistical analyses were performed in STATA to ensure reliability.

3. Results

3.1. Study selection

The initial database search identified 738 human studies and 1, 669 preclinical studies. After removing duplicates, titles and abstracts were screened, followed by full-text assessments. 25 preclinical studies and 10 human studies met the inclusion criteria for the meta-analysis. The detailed study selection process is presented in Fig. 1a and Fig. 1b

3.2. Descriptive results

3.2.1. Preclinical studies

The main characteristics of the 25 included preclinical studies (total animal sample size = 572) are summarized in STable 1 (Supplementary 4). Most studies were conducted in Asia ($n = 21$) [22–42], with others in the Americas ($n = 3$) [43–45] and Oceania ($n = 1$) [46]. Preclinical models included mice ($n = 21$) and rats ($n = 4$). Rat models exclusively involved Sprague-Dawley (SD) strains, while mouse models consisted of transgenic mice, C57BL/6, and Tau KO/C57BL/6 J strains. The preclinical models simulated AD through Aβ injections ($n = 7$) or transgenic models ($n = 18$). Curcumin administration methods included oral dosing ($n = 12$), gavage ($n = 8$), intraperitoneal injection ($n = 8$), and intravenous injection ($n = 1$). In the preclinical studies included in this meta-analysis, the Morris Water Maze (MWM) was the primary tool for assessing cognitive function, with consistent use across studies to evaluate memory acquisition and retention.

3.2.2. Human studies

Table 1 presents a summary of the 10 included human studies. All ten studies were double-blind designs. The sample size across the ten studies ranged from 18 to 96 participants, with a combined total of 531 participants. The study durations span from 4 weeks to 18 months. The mean participant age ranged from (61.0 ± 2.0) to (77.8 ± 7.7) years. Geographically, five studies were conducted in Oceania [47–51], three in the United States of America [52–54], and two in Asia [55,56]. Eight studies focused on older individuals without dementia [47–51,53,54,56], while two targeted patients with AD [52,55]. Daily curcumin dosages varied from 80 to 4000 mg. Seven studies reported positive effects of curcumin on cognitive outcomes, specifically memory and attention [47,48,50,51,53,54,56].

3.3. Meta-Analysis

3.3.1. Preclinical studies

3.3.1.1. Acquisition memory. Meta-analysis of Morris Water Maze (MWM) escape latency times (23 studies) showed significantly better acquisition memory in curcumin-treated groups (SMD = −1.78, 95 % CI: −2.12 to −1.43, I^2 = 69.4 %) (Fig. 2a). Subgroup analyses highlighted larger effect sizes in certain categories, such as by animal species, strain, gender, model type, and delivery route. Across all subgroups, the experimental group consistently outperformed the control group, with larger effect sizes observed in the following categories: species: mouse species (−1.89, 95 % CI: −2.30 to −1.43), 3xTg strain (−2.95, 95 % CI: −4.85 to −1.05), male gender (−2.20, 95 % CI: −2.84 to −1.57), 3xTgAD model (−2.948, 95 % CI: −4.851 to −1.045), intraperitoneal injection delivery (−2.61, 95 % CI: −3.49 to −1.73). Subgroup analyses suggest the delivery route may contribute to outcome heterogeneity (Supplementary 2).

Swim path, reported in four studies, showed a similar trend favoring curcumin treatment, though the limited sample size ($n = 4$) warrants cautious interpretation.

3.3.1.2. Retention memory. Retention memory, assessed primarily by target quadrant entries (13 studies), showed a significant improvement in the curcumin-treated group (SMD = 2.36, 95 % CI: 1.72 to 3.00, I^2 = 81.0 %) (Fig. 2b). Larger effect sizes were observed in B6C3-Tg strain (SMD = 4.77, 95 % CI: 2.41 to 7.13), male gender (SMD = 3.61, 95 % CI: 2.25 to 4.97), APP/PS1 model (SMD = 2.47, 95 % CI: 1.72 to 3.22), and intraperitoneal injection delivery (SMD = 4.50, 95 % CI: 3.03 to 5.97). Subgroup analyses indicated that gender and delivery route were major contributors to the between-subgroup heterogeneity in retention memory outcomes (Supplementary 2).

Additional retention memory indicators supported these findings. The ratio of platform zone dwelling time to total swimming time (11 studies) significantly favored curcumin treatment (SMD = 1.50, 95 % CI:1.09 to 1.90, I^2 = 59.7 %) (Supplementary 4 - SFigure 2B-1). Similarly, time in the target quadrant (7 studies) showed a positive trend (SMD = 2.09, 95 % CI: 1.18 to 3.00, I^2 = 84.2 %) (Supplementary 4 - SFigure 2B-2), though small sample sizes suggest caution.

3.3.2. Human studies

3.3.2.1. Cognitive outcomes. Five studies reported overall cognitive outcomes [49,51–53,55], which refer to broad measures of cognitive function, including global cognition, working memory, and executive function, as assessed through standardized neuropsychological tests. No statistically significant difference was observed between the curcumin and placebo groups (SMD = 0.14, 95 % CI: −0.78 to 1.07, I^2 =90.8 %). Subgroup analysis revealed significant cognitive improvement among AD patients in the placebo group (SMD = −0.62, 95 % CI: −1.19 to −0.05, I^2 = 0.0 %), but no significant effects among older individuals (SMD = −0.61, 95 % CI: −0.52 to 1.73, I^2 = 92.2 %). Fig. 3a illustrates these findings.

Meta-analyses showed significant improvements in specific cognitive domains: working memory (SMD = 1.01, 95 % CI: 0.15 to 1.87, I^2 = 88.3 %) and processing speed (SMD=0.37, 95 % CI: 0.07 to 0.67, I^2 =37.5 %). No significant effects were observed for executive function (SMD = 0.32, 95 % CI: −0.27 to 0.90, I^2 = 83.7 %). Forest plots for these analyses are shown in Figs. 3b, 3c, 3d

3.3.2.2. Adverse events. Meta-analysis of adverse reactions associated with curcumin indicated a statistically significant increase in adverse events compared to placebo (SMD = 2.40, 95 % CI: 1.37 to 4.21, I^2 = 44.1 %) (Supplementary 4 - SFigure 3).

3.4. Publication bias

In human studies, funnel plots and Egger's test revealed no publication bias in adverse event incidences ($p = 0.768$, $n = 9$) (Supplementary 3).

Table 1
The characteristics of the included human studies.

Author (year)	Study Design	Study Location	Study Duration	Sample Size & Intervention	Age	Man (%)	Study Population	Curcumin Product	Outcome Variable	Conclusions
Baum (2008)	RCT double-blind	Hong Kong, China	26 weeks	1 g/d: 8 4 g/d: 11 PBO: 8	1 g/d:69.0 ± 10.9 4 g/d: 73.4 ± 6.6 PBO:77.8 ± 7.7	NA	AD	Powder or capsule	MMSE, adverse event	No differences in MMSE scores. Adverse events: gastrointestinal side effects, respiratory tract infections, dizziness, delusional, edema, and hearing impairment.
Ringman (2012)	RCT double-blind	USA	24–48 weeks	2 g/d: 9 4 g/d: 10 PBO: 11	2 g/d: 76.7 ± 5.6 4 g/d: 75.3 ± 6.9 PBO: 70.2 ± 12.4	36.7	AD	Cur C3 complex®	ADAS-Cog; NPI; MMSE; adverse event	There were no differences in all cognitive measures. Adverse events: gastrointestinal side effect.
Cox (2015)	RCT double-blind	Australia	4 weeks	80mg/d: 30 PBO: 30	80mg/d:67.6 ± 4.5 PBO: 69.4 ± 6.6	36.7	Healthy older population	Longvida® Optimized Cur	The Computerized Mental Performance Assessment System; DASS	Cur significantly enhanced cognitive processes and had a significant beneficial effect on the change in mood induced by the mental challenge.
Rainey-Smith (2016)	RCT double-blind	Australia	52 weeks	1.32 g/d: 39 PBO: 57	66.0 ± 6.6	32.0	Community-dwelling older adults	Biocurcumax®	MoCA; RAVLT; WAIS-R; COWAT; DASS; adverse event	No differences in all cognitive measures and self-reported measures of depressive and anxiety-related symptoms.
Santos-Parke (2018)	RCT double-blind	USA	12 weeks	400mg/d: 20 PBO: 19	400mg/d:63.0 ± 2.0 PBO: 61.0 ± 2.0	53.8	Healthy men and postmenopausal women	Longvida®	NIH Toolbox-Cognition Battery evaluate processing speed, executive function, working memory, episodic memory, language, fluid cognition, crystallized cognition	12 weeks of cur supplementation does not improve motor and cognitive functions in healthy middle-aged and older adults.
Small (2018)	RCT double-blind	USA	78 weeks	180mg/d: 21 PBO: 19	180mg/d:63.1 ± 8.4 PBO: 62.9 ± 9.4	45.0	Middle-aged and older adults	Theracumin®	Buschke SRT; BVMT-R; BDI, adverse events	Cur significantly improved memory performance and depression status. Adverse events: gastrointestinal side effects
Kuszewski (a) (2020)	RCT double-blind	Australia	16 weeks	160mg/d:31 PBO: 32	160mg/d:65.7 ± 1.0 PBO: 65.8 ± 1.4	54.3	Overweight or Obesity	Brain Active™ (Longvida ®)	NIH Toolbox-Cognition Battery evaluate processing speed, executive function, working memory, episodic memory, language, fluid cognition, crystallized cognition	Cur improved vigour compared to placebo and reduced SMCs compared to no cur treatment.
Kuszewski (b) (2020)	RCT double-blind	Australia	16 weeks	160mg/d:31 PBO:32	160mg/d:65.7 ± 1.0 PBO: 65.8 ± 1.4	54.3	Overweight or Obesity	Brain Active™ (Longvida ®)	NIH Toolbox-Cognition Battery evaluate processing speed, executive function, working memory, episodic memory, language, fluid cognition, crystallized cognition	Cur performance of a verbal memory test compared with placebo in males only.
Cox (2020)	RCT double-blind	Australa	12 weeks	80mg/d: 42 PBO: 43 12weeks: 80mg/d: 39 PBO: 40	80 mg/d: 67.8 ± 6.0 PBO: 68.4 ± 6.7	50.0	Healthy older adults	Longvida®	MMSE, BDI-II, MoCA, NART, STAI-T, POMS, DATT, vMWM, Serial Subtractions, AFT	Cur improves working memory and mood as well as the possibility of learning in healthy individuals.
Khanna (2022)	RCT double-blind	India,	4.3 weeks	500mg/dCGM:6 500mg/d cur: 6 PBO: 6	46.6 ± 3.5	66.7	Healthy individuals	CurQfen®	AVRT, working memory	CGM improves memory improvements and fatigue reduction.

Note: cur: curcumin; Cur: Curcumin; AD: Alzheimer Disease; RCT: Randomized Controlled Trial; NA: Not Available; PBO: placebo; MMSE: Mini-Mental State Examination; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; NPI: Neuropsychiatric Inventory; DASS: Depression Anxiety Stress Scales; MoCA: Montreal cognitive assessment; RAVLT: Rey Auditory Verbal Learning Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised; COWAT: the Controlled Oral Word Association Test; Buschke SRT: Buschke Selective Reminding Test; BVMT-R: Brief Visuospatial Memory Test-Revised; BDI: Beck Depression Inventory; AFT: Arrow Flankers Task; NART: National Adult Reading Test; STAI-T: State-Trait Anxiety Inventory-Trait; POMS: Profile of Mood States; DATT: Divided Attention Task Test; vMWM: Virtual Morris Water Maze; AVRT: Audio-Visual Reaction Time.

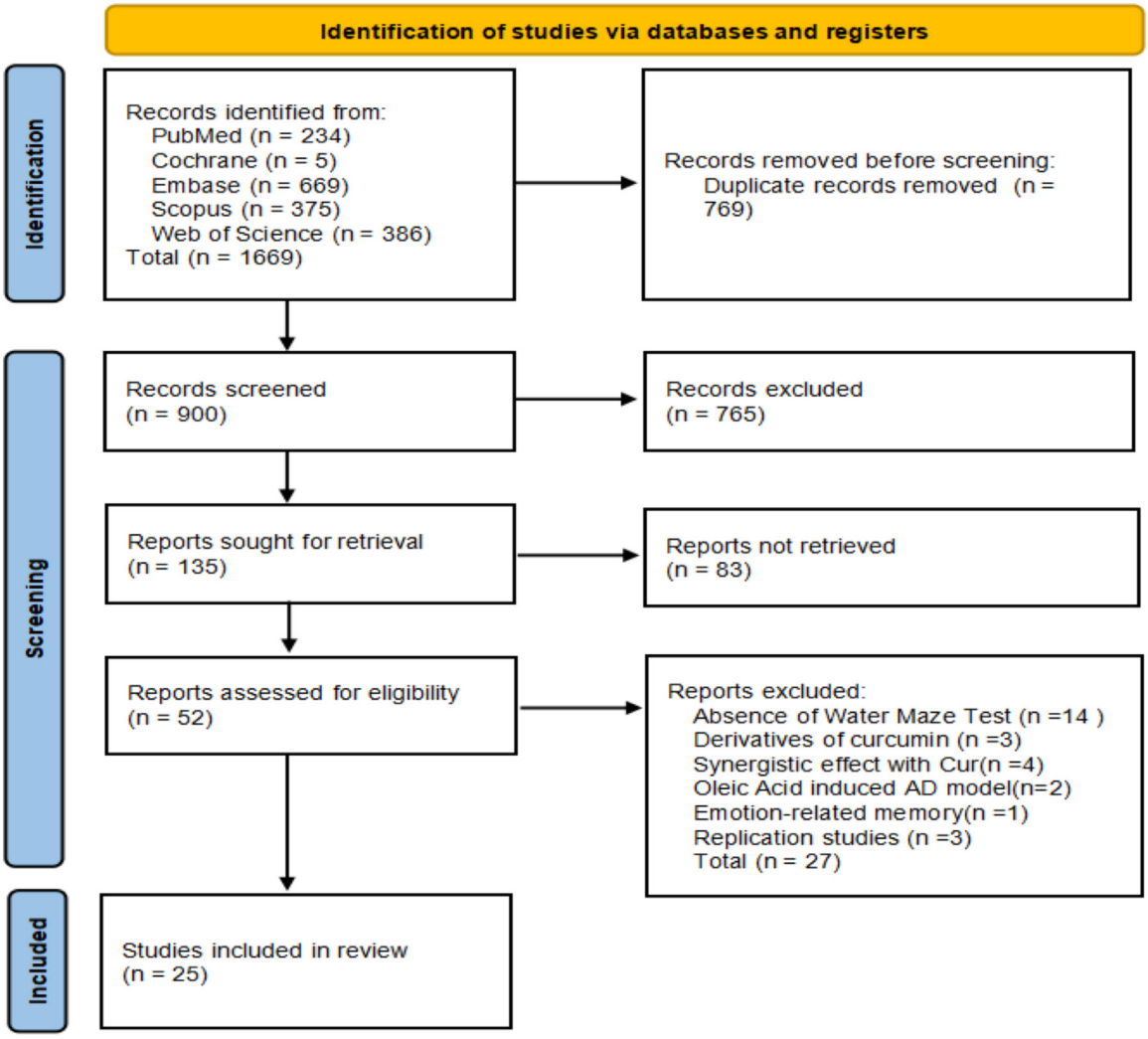

Fig. 1a. Flow diagram of preclinical study selection process.

In contrast, funnel plots for preclinical studies indicated potential publication bias for key outcomes, corroborated by Egger's regression test, which showed significant small-study effects ($p < 0.05$) (Supplementary 3).

3.5. Risk of bias assessment

3.5.1. Preclinical studies

Preclinical studies, evaluated using SYRCLE's Risk of Bias tool, showed concerns regarding selection bias, performance bias, and detection bias. These issues stemmed from inadequate reporting of allocation concealment, random housing, blinding of caregivers and/or investigators, and blinding of outcome assessments (STable 2A).

3.5.2. Human studies

The Cochrane Risk of Bias tool revealed a low risk of bias in randomization and blinding domains for most human studies. However, some studies raised concerns about missing outcome data and reporting bias [47,49,54]. Details are provided in STable 2B

4. Discussion

This study integrates findings from both preclinical and human research on curcumin's cognitive effects. In preclinical studies, curcumin demonstrated notable enhancements in memory acquisition and retention in AD models, suggesting potential neuroprotective mechanisms of curcumin. In contrast, human studies showed limited benefits on overall cognitive function, although subgroup analyses suggested improvements in working memory and processing speed.

Several factors may contribute to these discrepancies. First, curcumin exhibits poor oral bioavailability in humans due to rapid metabolism, low solubility, and systemic elimination, which limits its effective concentration in the brain [3,11]. Second, preclinical models typically represent simplified or early-stage disease and may not reflect the full pathological complexity and comorbidities observed in human AD populations [57]. Third, the clinical trials included in this review varied widely in formulation, dosage, duration, and cognitive outcome assessments, which may have introduced methodological heterogeneity and reduced comparability [16].

In addition to these methodological and pharmacokinetic factors, discrepancies in the specific cognitive domains assessed across species may also contribute to translational inconsistencies. This issue is further discussed in the following section.

4.1. Preclinical studies

Preclinical studies consistently demonstrated improvements in memory acquisition and retention metrics. These cognitive benefits are likely mediated through multiple mechanisms, including regulation of the

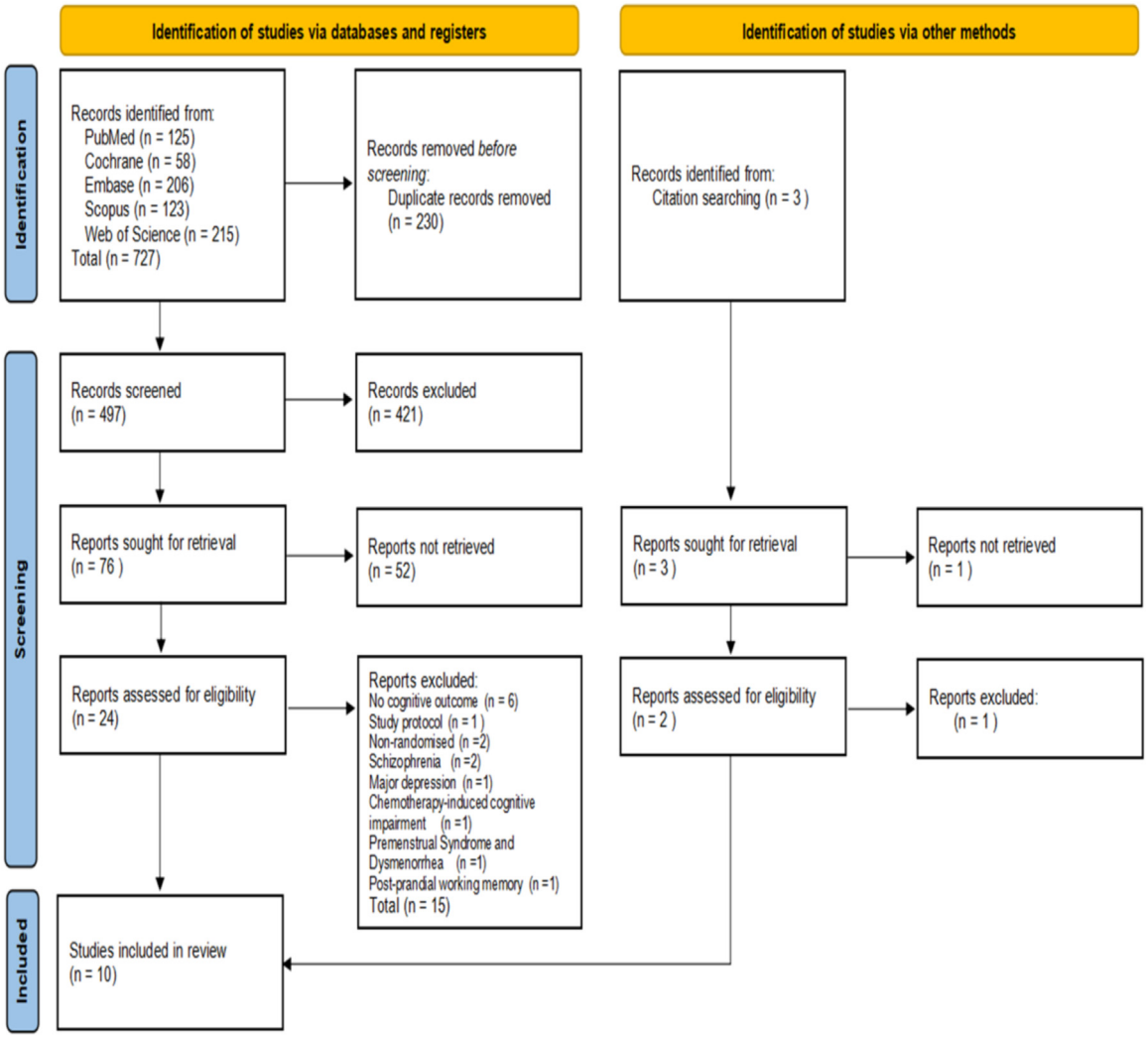

Fig. 1b. Flow diagram of human study selection process.

AMPK/mTOR pathway to enhance autophagy [58,59], enhancement of synaptic plasticity to strengthen neural connectivity [60,61], Curcumin has been shown to modulate several neurotransmitter systems, including increasing acetylcholine availability, enhancing nitric oxide signaling, and regulating monoamines such as dopamine and serotonin [62,63]. These neurotransmitters play essential roles in synaptic plasticity, learning, memory, and emotional processing. These findings underscore curcumin's dual potential as both a cognitive intervention and a research tool for elucidating neuroprotective mechanisms. Translating these insights into clinical trials could enhance the design of curcumin-based interventions, optimizing factors such as formulation, dosage, and treatment duration to maximize its therapeutic efficacy in cognitive aging.

4.2. Human studies

Despite promising results from preclinical models, the cognitive benefits of curcumin in humans, particularly in AD patients, remain inconclusive. Subgroup analyses showed that AD patients receiving curcumin had lower overall cognitive scores than those in the placebo group. Among the two included studies on AD, both suggested potential negative cognitive impacts of high-dose curcumin [52,55], consistent with findings by Zhu et al. [15]. Conversely, another meta-analysis reported no significant differences between curcumin and placebo groups in AD patients [64].

Several factors may contribute to these discrepancies: Firstly, the limited number of studies (n = 2) and participants (n = 60) reduces statistical power and increases variability. Secondly, considerable variation in curcumin dosage (ranging from 80 to 4000 mg/day) and treatment duration (from 4 weeks to 18 months) across studies may have contributed to inconsistent findings. Some trials with lower doses or shorter durations may have been insufficient to produce measurable effects, while high-dose interventions, although potentially more effective, often led to gastrointestinal adverse events (e.g., nausea, diarrhea), which reduced participant adherence and compromised efficacy. Thirdly, curcumin's neuroprotective properties, such as anti-inflammatory [65–67] and antioxidant effects [68,69], may be less effective in advanced AD stages, where neuronal damage is irreversible. Fourthly, drug interactions- concomitant treatments in AD patients may obscure or counteract curcumin's therapeutic effects. While curcumin is generally considered safe, its role as a cognitive enhancer requires further validation through well-designed, large-scale clinical studies to clarify its suitability for different stages of cognitive decline.

Furthermore, the high heterogeneity observed in human trials (I^2 values up to 90 %) likely stems from multiple methodological and clinical differences. These include variability in curcumin formulations (e.g., conventional vs. enhanced bioavailability types such as Theracurmin or nanoparticles), dosages, and treatment durations. Addition-

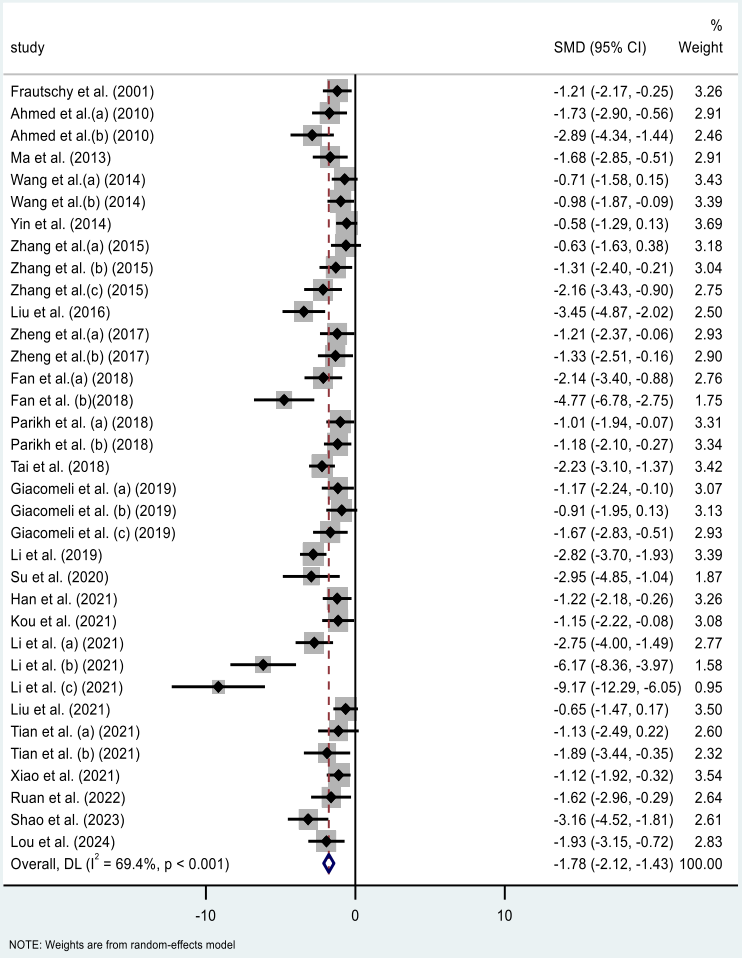

Fig. 2a. Forest plot of acquisition memory_scape latency time.

ally, participants differed in baseline cognitive status (e.g., healthy older adults, or AD), and diverse neurocognitive tests were used to assess outcomes, ranging from MMSE and MoCA to domain-specific batteries.

Although subgroup analyses were conducted to isolate effects by the cognitive domain (e.g., working memory, processing speed), such heterogeneity limits direct comparisons across trials. Differences in curcumin pharmacokinetics and central nervous system bioavailability across formulations further complicate interpretation. These factors likely explain the inconsistent findings in global cognitive outcomes and highlight the need for future studies to standardize formulations, stratify participants by cognitive status, and harmonize cognitive assessments to improve comparability and evidence quality.

In addition to clinical outcomes, emerging human studies have begun exploring curcumin's effects on Alzheimer's-related biomarkers. One RCT using FDDNP-PET imaging observed decreased tracer binding in the hippocampus and amygdala after 18 months of curcumin supplementation, suggesting a possible reduction in amyloid and tau burden. Another study reported reduced plasma levels of Aβ40 and Aβ42. However, no studies to date have assessed cerebrospinal fluid (CSF) biomarkers or used amyloid- or tau-specific PET tracers. These early findings are limited in scale but offer preliminary support for curcumin's central activity, underscoring the need for biomarker-integrated trials to better elucidate its mechanisms in humans [52,54].

4.3. Cross-Species comparisons

While both preclinical and clinical studies suggest the cognitive benefits of curcumin, they often assess different cognitive domains. Most in vivo animal studies focus on learning and spatial memory, commonly evaluated using behavioral paradigms such as the Morris water maze [60,61]. In contrast, human studies tend to evaluate working memory, processing speed, and executive function, using standardized neuropsychological tests [64].

These differences in outcome domains may contribute to discrepancies in efficacy observed between species, even though these functions may share overlapping neurobiological mechanisms. In vivo animal studies have demonstrated that curcumin enhances synaptic plasticity and dendritic complexity in brain regions involved in cognition, such as the hippocampus and cortex [60,61]. Additionally, curcumin modulates neurotransmitter systems—including nitric oxide and monoaminergic signaling—which are implicated in both memory and mood regulation [62,63].

Therefore, aligning cognitive outcome measures between preclinical and clinical studies is essential. Harmonizing the domains assessed, along with shared mechanistic targets, may enhance the translational relevance of animal data and improve clinical applications of curcumin for cognitive aging.

Beyond cognitive domains, another important aspect of translational research lies in comparing the dosing regimens used in animal and hu-

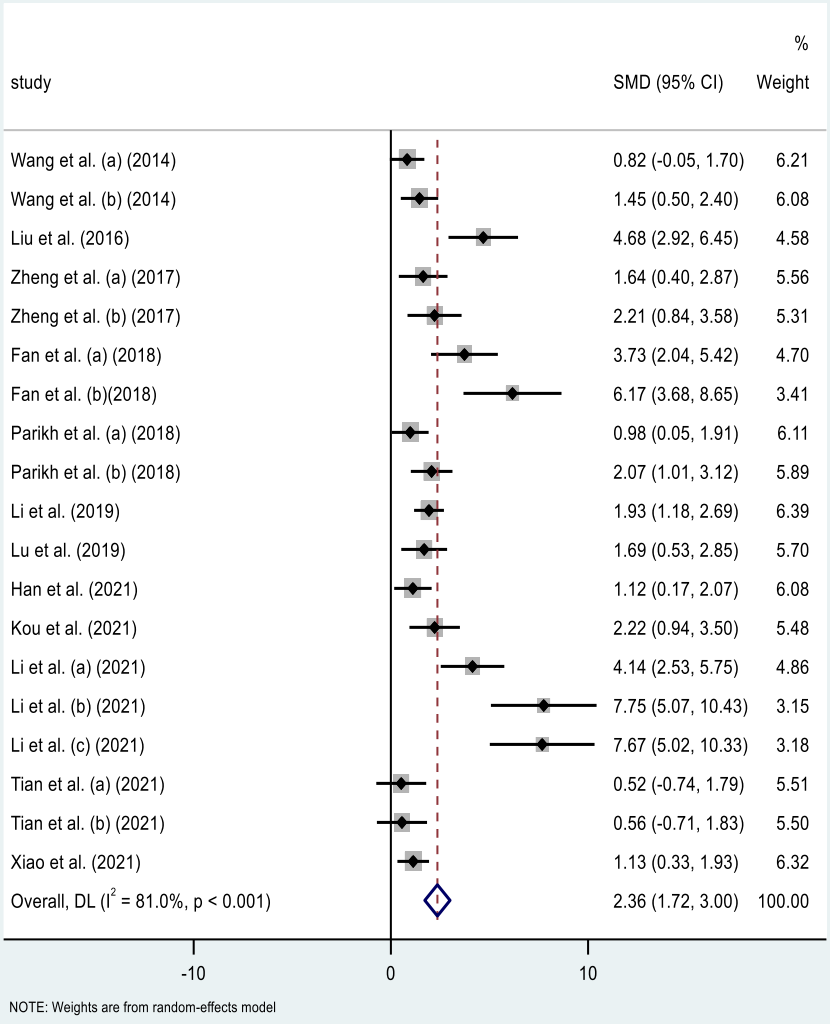

Fig. 2b. Forest plot of retention memory_target quadrant entries.

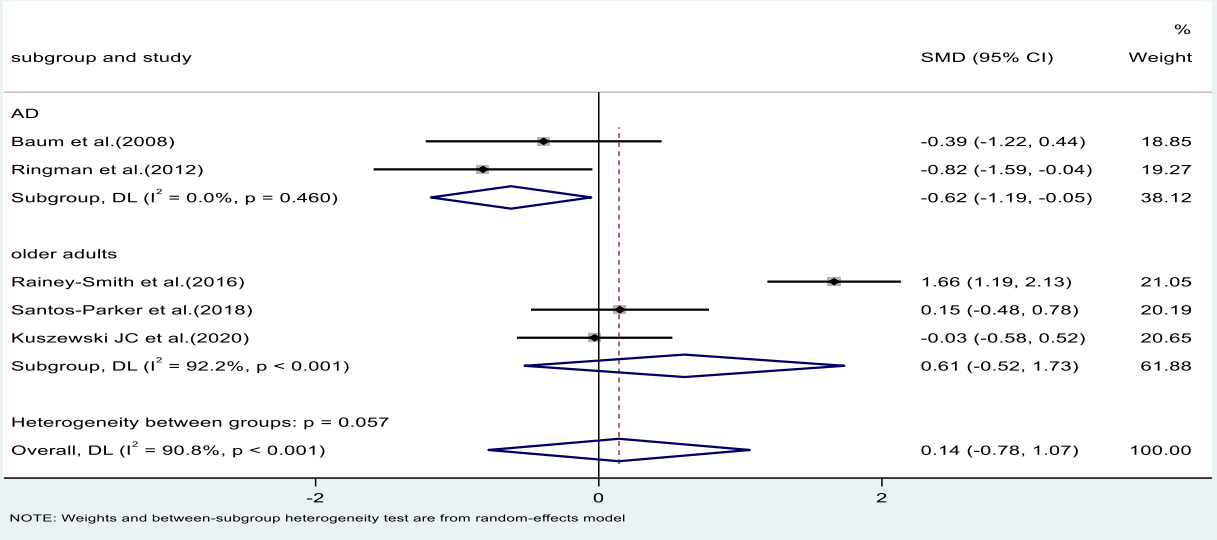

Fig. 3a. Forest plot of overall cognitive function.

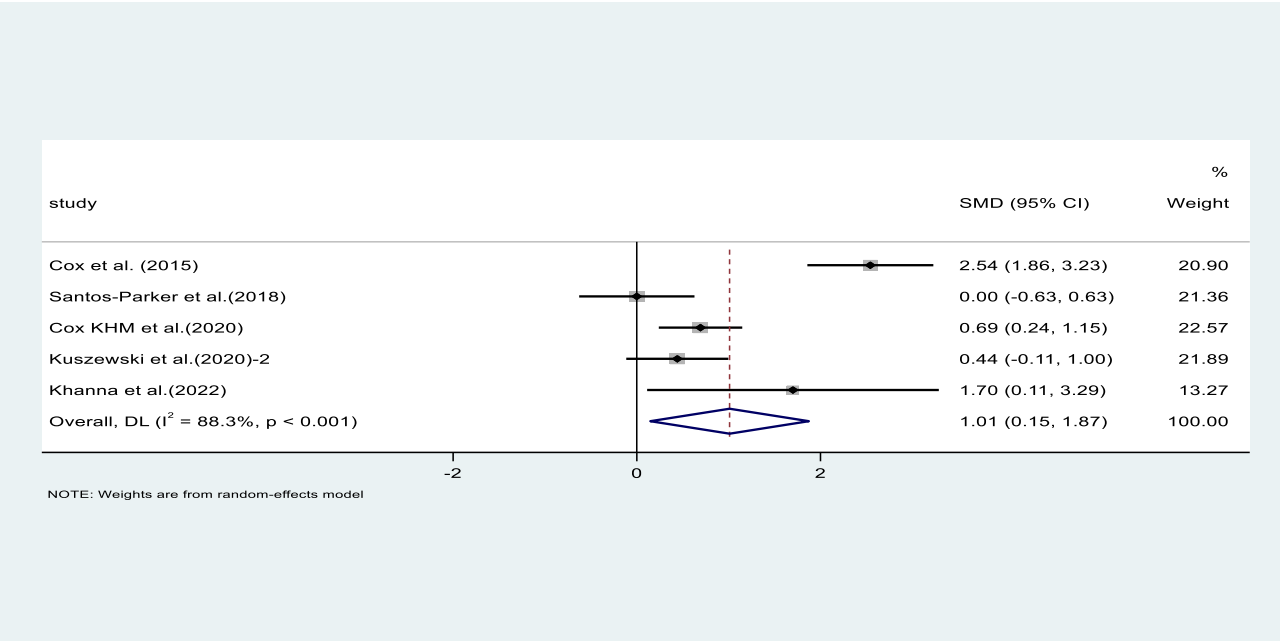

Fig. 3b. Forest plot of working memory.

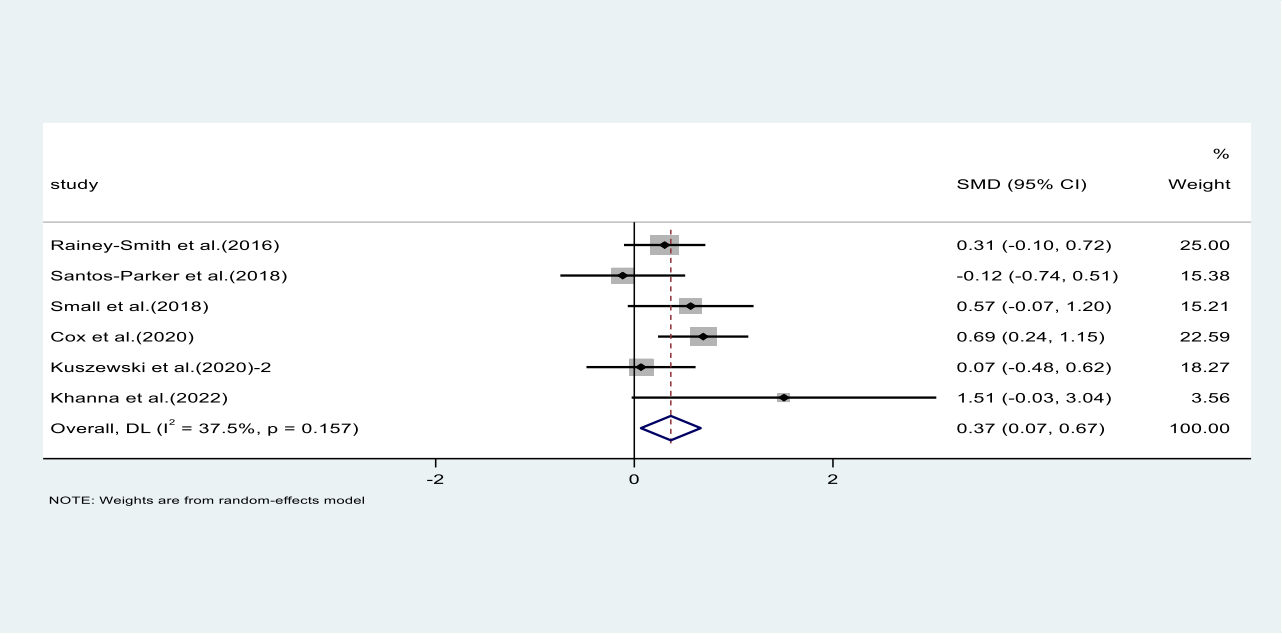

Fig. 3c. Forest plot of processing speed.

man studies. The comparison between curcumin dosages in animal models and human clinical trials remains a key translational challenge. In rodent studies, curcumin is typically administered at 50–300 mg/kg/day. According to standard allometric scaling based on body surface area normalization, as proposed by Nair and Jacob, this corresponds to a human equivalent dose (HED) of approximately 570–3400 mg/day for a 70-kg adult [70]. However, due to interspecies differences in metabolism, first-pass hepatic clearance, and curcumin's inherently low oral bioavailability, direct translation is not straightforward. To achieve comparable systemic exposure, human trials often require the use of bioavailability-enhanced formulations such as nanoparticles, and phospholipid complexes. These pharmacokinetic differences should be considered when interpreting preclinical efficacy in the context of human dosing.

4.4. Adverse events

We observed a statistically significant difference in adverse events incidence, with sensitivity analysis identifying the Rainey-Smith study [49] as a key source of heterogeneity. Excluding this study reduced the heterogeneity, emphasizing the impact of intervention design on safety outcomes.

Several factors may explain this divergence. Firstly, the administration of 500 mg of Biocurcumax^{TM}, which is considered a high dose, three times daily likely contributed to gastrointestinal side effects, such as nausea and diarrhea [64,71]. Previous research has shown that curcumin's side effects are dose-dependent. At lower concentrations, curcumin exhibits antioxidant properties, while at higher concentrations,

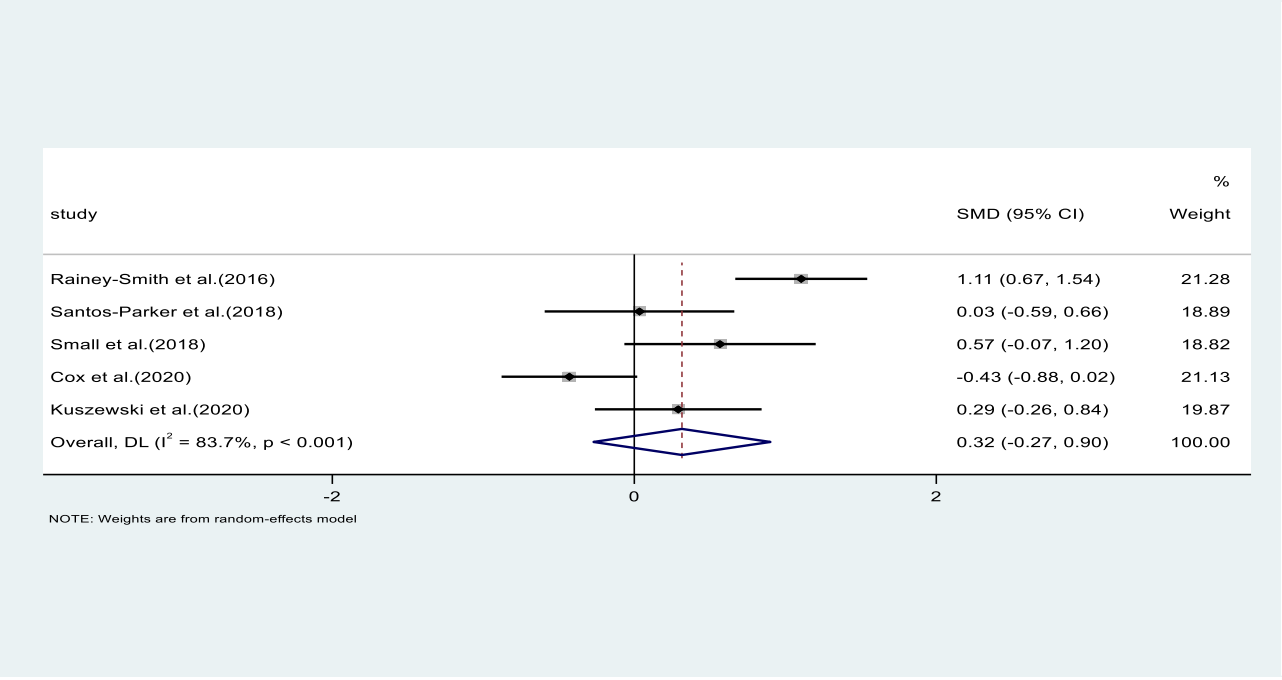

Fig. 3d. Forest plot of executive function.

it may shift toward pro-oxidative effects, increasing intracellular reactive oxygen species, which can lead to localized inflammation, gastrointestinal irritation, and discomfort [72,73]. Secondly, frequent dosing schedules may reduce adherence, exacerbating adverse event rates [16]. Thirdly, high-dose regimens challenge treatment tolerability, amplifying physical discomfort, even in double-blind trials designed to control for psychological biases.

These findings underscore the need for systematic evaluations of curcumin formulations, dosages, and administration methods to enhance both safety and efficacy in future studies. Optimizing intervention strategies may help mitigate adverse effects while preserving curcumin's potential therapeutic benefits.

5. Limitations

This study integrates data from animal and human studies, offering valuable insights; however, several limitations must be acknowledged. Firstly, in human studies, small sample sizes, short follow-up durations, and participant variability hinder the ability to draw robust conclusions about curcumin's long-term cognitive benefits. These factors contribute to inconsistencies in clinical findings and reduce statistical power. In animal models, the reliance on transgenic and Aβ-injection models of AD may not fully replicate the complexity and pathology of human AD, limiting the translational relevance of preclinical findings. Differences in disease progression, immune response, and metabolism between species further challenge the direct applicability of these results to human populations. Lastly, publication bias was detected in the animal meta-analysis, potentially inflating effect sizes and compromising reliability. The tendency to publish positive findings over negative or null results may distort the overall evidence base, necessitating cautious interpretation of preclinical data. Addressing these limitations through larger, long-term human trials, improved animal models that better reflect AD pathology and strategies to mitigate publication bias will be crucial for refining our understanding of curcumin's role in cognitive aging.

6. Conclusions

This meta-analysis highlights significant gaps and contradictions in current evidence regarding curcumin's potential for cognitive aging. Preclinical in vivo evidence supports the potential of curcumin to enhance cognitive function in AD models. However, findings from human trials remain inconsistent and heterogeneous, with only domain-specific benefits observed in some studies. Variability in dosage, treatment duration, formulation type, and outcome assessments likely contribute to these inconsistencies. Moreover, higher doses of curcumin may lead to adverse gastrointestinal effects that limit adherence and offset potential cognitive benefits. Given these limitations, no definitive clinical recommendations regarding curcumin supplementation for cognitive aging can be made at this stage. Well-designed, large-scale, and standardized randomized controlled trials are urgently needed to determine curcumin's efficacy, optimal dosing strategies, and safety profile in human populations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Lirong Yu: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Na Li:** Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Bin Li:** Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Kaisy Xinhong Ye:** Writing – review & editing, Visualization, Validation, Investigation. **Jiuyu Guo:** Writing – review & editing, Software, Formal analysis, Data curation. **Jiatong Shan:** Writing – review & editing, Software, Formal analysis, Data curation. **Luwen Cao:** Writing – review & editing. **Mei Song:** Writing – review & editing. **Yanyu Wang:**

Visualization, Validation, Investigation. **Tih-Shih Lee:** Writing – review & editing. **Andrea B Maier:** Supervision, Resources. **Lei Feng:** Writing – review & editing, Supervision, Resources, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100248.

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