Cognitive effects of nutraceutical chocolate-based formulations enriched with *Bacopa monnieri*, *Centella asiatica*, and cocoa (*Theobroma cacao*) flavanols - a systematic review of neurobiological mechanisms and clinical evidence

R.A.C. Haily Seneviratne

haily.seneviratne@wyb.ac.lk

Department of food Science and Technology, Wayamba University of Sri Lanka https://orcid.org/0009-0001-0317-137X

Ba X Hoang

Department of Surgery, Keck School of Medicine of USC https://orcid.org/0000-0003-2712-9747

Systematic Review

Keywords: Bacopa monnieri; Centella asiatica, Theobroma cacao, cocoa flavanols, Memory melt functional chocolate, cognitive enhancement, neuroprotection, nutraceuticals, nutritional neuroscience

Posted Date: June 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9906053/v1

Additional Declarations: The authors declare no competing interests.

Abstract

Background

Age related cognitive decline, stress-related memory disturbances, neurovascular changes and dementia increasingly influence cognitive performance across the lifespan. This leads to growing interest in nutritional approaches that may help protect brain functions such as supporting memory, learning, and executive function. Traditional Ayurvedic herbs such as *Bacopa monnieri* (Lunuwila) and *Centella asiatica* (Gotu kola), along with flavanol-rich cocoa derived from *Theobroma cacao* (Cocoa/Kokowa), have each been studied for possible antioxidant, anti-inflammatory, and cognitive benefits. However, evidence supporting their combined use in functional foods like herbal chocolate is still insufficient.

Objective

This systematic review aimed to summarise research published between 2006 and 2026 on the cognitive and neuroprotective effects of *Bacopa monnieri, Centella asiatica*, cocoa flavanols, and selected bioactive compounds that are in herbal chocolate formulations combining *Bacopa monnieri* and *Centella asiatica*, such as commercially available *Memory melt chocolate*.

Methods

A systematic review was conducted following PRISMA 2020 guidelines. Nine databases (PubMed, MEDLINE, Embase, Scopus, SCI, CENTRAL, CINAHL, CLIB, PsycInfo) were searched for publications from January 2006 to April 2026 with no language restriction. Included studies comprised randomised controlled trials (RCTs) reporting validated cognitive outcomes in human participants, plus preclinical (animal/*in vitro)* studies for mechanistic synthesis. Risk of bias of RCT studies were assessed using Cochrane RoB-2 tool. Studies that did not report cognitive or neurobiological outcomes, non-peer-reviewed publications, review articles, conference abstracts, and studies lacking sufficient methodological detail were excluded. Due to substantial heterogeneity in interventions, populations, doses, and outcome measures, a narrative synthesis was performed; meta-analysis was not conducted.

Results

Seventeen RCT studies met inclusion criteria. Among *Bacopa monnieri* trials (n = 9 RCTs), consistent improvements were observed in episodic memory, working memory, attention, and executive function in both healthy adults and older individuals, primarily at 300 mg/day over 8 to 12 weeks, with cholinergic modulation (AChE inhibition up to 27%) as a key mechanism. Cocoa flavanols (n = 5 RCTs) show moderate clinical support, particularly dose-dependent improvements in executive function, processing speed cerebral blood flow, likely through vascular and neurotrophic mechanisms. For *Centella asiatica* (n = 2 RCTs), while human trials have provided mixed results-often due to the limited funding landscape for large-scale nutraceutical research compared to pharmaceutical trials-experimental studies confirm strong neuroprotective potential. β-caryophyllene, a cocoa-associated sesquiterpene, show promising anti-inflammatory and neuroprotective activity in *in vitro* and *in vivo* models.

Conclusions

Overall, evidence supports the cognitive benefits of these ingredients, validated by centuries of traditional use and a robust safety profile. Although RCT data for cocoa flavanols and *Bacopa monnieri* are moderate, the limited evidence for *Centella asiatica* often reflects constrained funding for nutraceuticals rather than a lack of efficacy. This contrast is notable compared with approved pharmaceuticals, which offer modest benefits and side effects despite heavy investment. This cocoa based formulation remains a biologically plausible, safe, and cost-effective strategy for cognitive support while needed rigorous evaluation in well-designed clinical trials. Standardisation of extracts, cognitive outcome measures, and reporting is needed to advance this field.

Introduction

Cognitive health impairment represents a broad and growing spectrum that includes age-related cognitive decline, mild cognitive impairment (MCI), stress-related memory dysfunction, dementia and vascular-associated cognitive changes. Dementia alone affected more than 57 million individuals worldwide in 2021 (World Health Organization, 2025), with over 60% of cases occurring in low- and middle-income countries, according to the World Health Organization (WHO). And it is projected to exceed 150 million cases by 2050 (WHO, 2017). In addition, Population-based analyses estimate that Mild Cognitive Impairment (MCI) affects approximately 12–18% of adults older than 60 years (*Mild Cognitive Impairment (MCI)*, no date), representing a major at-risk group for future dementia and functional decline. Even among cognitively healthy individuals, gradual age-related reductions in memory, processing speed, and executive function are widely documented with advancing age and contribute to reduced independence, work capacity, and quality of life in later years (Harada, Natelson Love and Triebel, 2013).

Beyond ageing, chronic psychological stress represents an under-recognized contributor to cognitive vulnerability. Prolonged glucocorticoid exposure - including cortisol and corticosterone - disrupts hippocampal plasticity, impairs synaptic signaling, and reduces learning efficiency in both clinical and subclinical populations (Kim, Song and Kosten, 2006). Concurrently, vascular and metabolic factors - including endothelial dysfunction, insulin resistance, and chronic cerebral hypoperfusion - are implicated in up to 15% of dementia cases and are broadly relevant to cognitive ageing (Gorelick et al., 2011; Iadecola and Gottesman, 2019; Livingston et al., 2020). These converging pathophysiological mechanisms - neuroinflammation, oxidative stress, synaptic

dysfunction, and neurovascular dysregulation - highlight the need for multi-target preventive strategies acting upstream of irreversible neurodegeneration (Heneka et al., 2015; Butterfield and Halliwell, 2019).

Against this backdrop, nutraceutical interventions have attracted growing scientific interest as accessible, low-risk, and multi-target approaches to cognitive health maintenance. Importantly, currently approved pharmacological treatments for Alzheimer's disease and dementia offer only modest clinical benefit and frequently carry significant side-effect burdens, further motivating the investigation of natural alternatives (Walsh et al., 2024). In this context, *Bacopa monnieri*, *Centella asiatica*, and cocoa-derived flavanols (*Theobroma cacao*) represent three botanically and mechanistically distinct ingredients with individually promising cognitive and neuroprotective profiles.

Bacopa monnieri (Brahmi) and *Centella asiatica* (Gotu kola) are classical Medhya Rasayana herbs in Ayurvedic medicine, traditionally used to strengthen intellect, memory, and emotional stability (Orhan, 2012; Jiang et al., 2025). Modern clinical evidence confirms that standardized *Bacopa* extract significantly improves verbal learning, memory recall, attention, and processing speed in healthy adults and older populations (Raghav et al., 2006a; Peth-Nui et al., 2012; Valotto Neto et al., 2024). A meta-analysis of nine RCTs (n = 437) corroborated faster reaction time and attentional performance following *Bacopa* supplementation (Kongkeaw et al., 2014). *Centella asiatica* demonstrates robust preclinical neuroprotective effects in rodent models of Alzheimer's disease and ageing, including improved object recognition, reduced oxidative stress, and enhanced synaptic density (Matthews et al., 2019; Hack et al., 2025), although direct human RCT data remain limited. Cocoa flavanols add complementary neurovascular and antioxidant mechanisms: dose-dependent improvements in cerebral blood flow, insulin sensitivity, and executive function have been reported in elderly and MCI populations (Grassi et al., 2008; Desideri et al., 2012; Mastroiacovo et al., 2014). Notably, β-caryophyllene - a sesquiterpene present in cocoa - acts as a selective CB_2 receptor agonist with anti-inflammatory and neuroprotective properties, preventing memory impairment in rodent neurotoxicity and ageing models (Alberti et al., 2017; Ricardi et al., 2025).

Chocolate-based nutraceutical formulations combining these ingredients - such as those enriched with Ayurvedic nootropics and flavanol antioxidants - represent a novel and commercially emerging delivery system for cognitive health applications (Memory Melt Chocolate, 2026). However, despite individually promising evidence, no systematic review has yet integrated the clinical and mechanistic evidence for these three bioactive classes within a unified formulation framework, nor evaluated the plausibility of their combined synergistic effects.

This systematic review therefore aims to critically synthesize available evidence from randomized controlled trials (RCTs) and preclinical mechanistic studies on the cognitive and neuroprotective effects of *Bacopa monnieri*, *Centella asiatica*, cocoa flavanols, and their key bioactive constituents, conducted in accordance with PRISMA 2020 guidelines.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021)

Study protocol registration

The review protocol was prospectively registered with PROSPERO prior to data extraction (registration pending final publication number) in accordance with PRISMA-P 2015 guidance. No ethical approval was required, as no primary data collection was undertaken. The full protocol is accessible via the PROSPERO record and a PDF supplement linked therein.

Study protocol

Systematic database searches were conducted by H. Seneviratne across nine electronic databases: PubMed/MEDLINE, MEDLINE via Ovid, Embase via Ovid, Scopus, Web of Science / Science Citation Index, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, the Cochrane Library (CLIB), and PsycInfo. Searches spanned 1 January 2006 to 22 April 2026 with no language restrictions. The search strategy combined controlled vocabulary (MeSH, Emtree) and free-text keywords covering the intervention terms (*Bacopa monnieri*, *Centella asiatica*, cocoa flavanols, *Theobroma cacao*, epicatechin, β-caryophyllene) with cognitive outcome terms (cognition, memory, attention, executive function, working memory, neuroprotection). Syntax was adapted to each database interface. No publication-type or language limits were applied at the search stage. Additional records were identified through forward citation searching (n = 17) and backward reference-list checking (n = 13) of all included studies. Gray literature, conference abstracts without full data, editorials, and non-peer-reviewed sources were excluded.

Selection Criteria

Selection criteria were guided by the Population, Intervention, Comparator, Outcomes, and Study design (PICO) framework. Included studies investigated supplementation with *Bacopa monnieri*, *Centella asiatica*, cocoa flavanols, dark chocolate with quantified flavanol content, or related isolated bioactives (e.g., bacosides, asiaticoside, epicatechin, β-caryophyllene) in human participants of any age, including healthy adults, older adults, students, and those with mild cognitive impairment or stress-related cognitive decline. Studies were required to report validated cognitive or neurobiological outcomes. No restriction was applied on dose, formulation, intervention duration, sex, ethnicity, or clinical setting. Randomised controlled trials (RCTs), double-blind placebo-controlled trials, and controlled clinical trials were included for the primary clinical synthesis; animal and *in vitro* studies were included for mechanistic synthesis only. We excluded non-randomised trials, cohort studies (for primary synthesis), case reports or series, systematic reviews, meta-analyses, commentaries, editorials, conference abstracts without full data, and studies lacking relevant cognitive or neurobiological outcomes.

Data Extraction

All citations were consolidated and de-duplicated, yielding 1,867 unique records for screening (Fig. 1). Titles and abstracts were screened by one reviewer and checked by a second against pre-specified eligibility criteria. Full texts were obtained for 144 records; 146 reports (138 from databases, 8 from other methods) were assessed for eligibility. Data were extracted by one reviewer using a standardized form and independently verified by a second reviewer. Discrepancies were resolved by discussion. Extracted data included: author, year, country, study design, population, sample size, intervention, dose and duration, comparator, cognitive instruments, quantitative findings, and stated conclusions. Where required information was missing from published reports, corresponding authors were contacted.

Quality Review

Each included RCT was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. The following domains were evaluated: (D1) randomization process; (D2) deviations from intended interventions; (D3) missing outcome data; (D4) outcome measurement; and (D5) selection of the reported result. Each domain was rated Low, High, or Unclear risk of bias (labeled as 'some concerns'); an overall judgement was derived per the RoB 2 algorithm. Assessments were conducted in duplicate, with disagreements adjudicated by the guarantor overall Low risk-of-bias rating that reported statistically significant effects were identified and summarized. Due to the heterogeneity of interventions, populations, and outcome measures, meta-analysis was not performed; a structured narrative synthesis was used throughout.

Study-Level Outcomes

Study-level data are presented in aggregate in Tables 1–2 and qualitative summaries in Tables 3–4. Key data extracted for each study included: study year, participant characteristics (age, health status, proportion female), intervention composition and dose, comparator, sample size per arm, and intervention duration. Due to the heterogeneity of cognitive outcome instruments and analytical methods across included studies, we present the primary cognitive outcome for each study (e.g., AVLT delayed recall, TMT-A/B, working memory accuracy, Stroop interference, MMSE/MoCA), the direction and magnitude of effect, and the reported p-value or confidence interval. All statistically significant and null results are reported across all cognitive domains. Mechanistic and biomarker findings (e.g., AChE activity, BDNF, oxidative stress markers) are reported as secondary outcomes where available.

Results

Table 1. Summary of randomized controlled trials by intervention, dosage, duration, population, cognitive outcomes, and key results (including primary, secondary, and mechanistic findings; positive and null results shown)

Study	Intervention	Dose / Duration	Population	Cognitive domains	Primary outcomes (quantitative)	Secondary / Detailed outcomes	Temporal / dose effects	Mechanistic / Biomarker findings	Overall
Peth-Nui et al., 2012 (Peth-Nui *et al.*, 2012)	*Bacopa monnieri*	300 vs 600 mg/day, 12 wk	Healthy elderly (N=60)	Attention, WM, Processing speed	300 mg: ↑ continuity of attention & memory quality (P<0.001); both doses ↑ attention speed (P<0.01)	↑ digit-span backward (+1.4 vs +0.2; P<0.05); ↓ reaction time (P<0.05); ↑ power of attention (choice RT, P<0.01); 600 mg: ↑ memory processing speed (P<0.01)	Effects from wk 8–12; dose-dependent (300 vs 600 mg differences)	↓ erythrocyte AChE (−27%, P<0.05); sustained ↓ at 4, 8, 12 wk (P<0.001); cholinergic enhancement; possible BDNF/synaptic plasticity (preclinical)	Strong positive
Stough et al., 2008 (Stough *et al.*, 2008)	*Bacopa monnieri*	300 mg/day, 90 d	Healthy adults (N=62)	Working memory	↑ spatial WM accuracy (P<0.05)	↑ composite WM factor; ↑ auditory-verbal delayed recall (AVLT; group×time P=0.03, prior study)	Progressive over 90 days	—	Positive
Calabrese et al., 2008 (Calabrese *et al.*, 2008)	*Bacopa monnieri*	300 mg/day, 12 wk	Elderly (N=54)	Verbal memory, Executive	↑ AVLT delayed recall (P≈0.03); ↓ Stroop RT (P≈0.003)	↓ Stroop interference; ↓ CESD-10 depression (P<0.05); ↑ composite cognition (group×time P=0.01)	Gradual over 12 wk	—	Positive
Raghav et al., 2006 (Raghav, *et al.*, 2006)	*Bacopa monnieri*	250 mg/day, 12 wk	Adults (N=35)	Memory, Executive	↑ mental control; ↑ episodic memory; ↑ logical memory; ↑ paired associates (P<0.05)	Stronger effects in logical memory tasks and paired-associate learning.	Sustained over 12 wk	—	Positive
Crosta et al., 2020 (Crosta, *et al.*, 2020)	*Bacopa* + antioxidants	300 mg/day, 8 wk	Older adults (N=80)	Executive	↓ TMT-B (−21.0 s; 95%CI −26.8 to −15.2; P<0.0001); ↓ TMT-A (−6.9 s; P<0.0001)	↑ verbal fluency (+4.21 to +5.28 vs +1.07 words; P<0.001); placebo worsened; consistent Δ patterns	Rapid (≤8 wk)	↓ P300 latency (ERP); mitochondrial + NRF2 synergy; antioxidant additivity	Strong positive
Cicero et al., 2017 (Cicero *et al.*, 2017)	*Bacopa* combination	8 wk	Cognitive complaints (N=30)	Global cognition, Stress	↑ MMSE (P<0.05–0.01)	↓ PSQ stress index (P<0.05); ↓ SRDS depression (P<0.05); AVLT not assessed	Short-term	—	Positive
Morgan & Stevens, 2010 (Morgan and Stevens, 2010)	*Bacopa monnieri*	300 mg/day, 12 wk	Adults (N=81)	Episodic memory	↑ AVLT A4 (P=0.000), A5 (P=0.016), A6 (P=0.000), A7 delayed recall (P=0.001)	↑ total learning (P=0.011); ↓ retroactive interference (P=0.048); NS: CFT, MAC-Q, TMT	Progressive	—	Positive
Benson et al., 2014 (Benson *et al.*, 2014)	*Bacopa monnieri*	320–640 mg acute	Adults (N=17)	Executive, Stress	↑ cognition under stress (P<0.05)	↓ cortisol (P<0.05); ↑ memory under stress	Acute	HPA-axis modulation	Positive
Kumar et al., 2016 (Kumar *et al.*, 2016)	*Bacopa monnieri*	300 mg/day, 6 wk	Students (N=60)	WM, Attention	↑ WM; ↑ logical memory; ↓ distractibility (P<0.05)	Early onset effects		—	Positive

Wattanathorn et al., 2008 (Wattanathorn *et al.*, 2008)	*Centella asiatica*	250–750 mg/day, 2 mo	Elderly (N=28)	WM, Mood	↓ reaction time (P<0.05 at 750 mg)	↑ mood (self-reported, NS); ↑ N100 ERP amplitude (~21%, P<0.05)	Dose-dependent (higher dose effective)	Neural processing enhancement	Mild positive
Anista Fitriana et al., 2021 (Anisa Fitriana *et al.*, 2021)	*Centella asiatica*	250–750 mg/day, 12 wk	Dementia (N=62)	Memory	↑ memory (P=0.001)	↑ SOD (P=0.009); +exercise: ↑ SOD (P=0.031), ↑ memory (P=0.001), ↑ QoL		Antioxidant-mediated	Strong positive
Mastroiacovo et al., 2014 (Mastroiacovo *et al.*, 2014)	Cocoa flavanols	48–993 mg/day, 8 wk	Elderly (N=90)	Executive, Speed	↓ TMT-A (−8.6±0.4 vs −0.8; P<0.0001); ↓ TMT-B (−29.23 s vs +3.83: P<0.0001); ↑ verbal fluency (+7.97 vs +1.3 ; P<0.0001)		Strong dose-response	—	Strong positive
Baker et al., 2022 (COSMOS) (Baker *et al.*, 2022)	Cocoa extract	500 mg/day, 3 yr	Older adults (N=2262)	Global cognition	NS (mean diff +0.03; 95%CI −0.02–0.08; P=0.28)	No effect on TMT-B; no composite change	Long-term	—	Null
Desideri et al., 2012 (Desideri *et al.*, 2012)	Cocoa flavanols	45–990 mg/day, 8 wk	MCI (N=90)	Executive	Significant improvement (dose-dependent)	↓ insulin resistance; replicated strong TMT-A/B improvements (P<0.0001); ↑ verbal fluency	Dose-response	Metabolic–cognitive link	Positive
Field et al., 2011 (Field, Williams and Butler, 2011)	Cocoa flavanols	720 mg acute	Adults (N=30)	WM, Speed	↑ spatial WM accuracy (P<0.05)	↑ reaction-time accuracy (P<0.05); ↓ fatigue; mixed RT findings	Acute (within 2 h)	—	Acute positive
Suominen et al., 2020 (Suominen *et al.*, 2020)	Dark chocolate	86 vs 410 mg/day, 8 wk	Older adults (N=100)	Executive	NS TMT-A (Δ−4.6 vs −4.4 s; P=0.93); NS TMT-B (P=0.66)	NS verbal fluency; NS global cognition		—	Null
Bell et al., 2021 (Bell *et al.*, 2021)	β-caryophyllene	90 vs 180 mg/day, 8 wk	Elderly (N=52)	Memory	↑ memory vs baseline (P<0.05)	CFQ: ↓ 27–36% across subscales (P≤0.05); higher dose trend stronger	Dose-dependent trend	—	Positive

Abbreviations:

AChE, acetylcholinesterase; AVLT, Auditory Verbal Learning Test; BCP, β-caryophyllene; CESD-10, Center for Epidemiologic Studies Depression Scale (10-item); CFQ, Cognitive Failures Questionnaire; CFT, Category Fluency Test; HPA, hypothalamic–pituitary–adrenal; MAC-Q, Memory Assessment Clinics Questionnaire; MMSE, Mini-Mental State Examination; NRF2, nuclear factor erythroid 2–related factor 2; P300, P300 event-related potential; PSQ, Perceived Stress Questionnaire; QoL, quality of life; RT, reaction time; SOD, superoxide dismutase; SRDS, Self-Rating Depression Scale; TMT-A/B, Trail Making Test Parts A and B; VFT, Verbal Fluency Test; WM, working memory.

Table 2. Mechanistic (animal/*in vitro*) evidence relevant to cognitive domains. Key quantitative findings on neuroprotection, inflammation, neurogenesis, synaptic plasticity, and neurovascular function are summarized, linking molecular effects to functional and cognitive outcomes.

Study	Compound	Pathway	Model	Molecular effects	Functional outcome	Cognitive link
Nemetchek et al., 2016 (Nemetchek *et al.*, 2016)	*Bacopa* bacosides	Microglial inhibition (anti-inflammatory)	Activated microglial culture	↓ nitric oxide; ↓ TNF-α; ↓ IL-6 vs activated controls (P<0.05)	Direct suppression of activated microglia	Attenuates neuroinflammation → preserves cognition
Ar Rochmah et al., 2019 (Ar Rochmah *et al.*, 2019)	*Centella asiatica*	Neuroinflammation + neurotrophic signalling	Chronically stressed rats (600 mg/kg/day)	↓ hippocampal TNF-α; ↑ BDNF vs stress control (P<0.05); dose-specific effect at high-dose CA	Restoration of hippocampal neurotrophic balance	Memory recovery via plasticity restoration
Speers et al., 2021 (Speers *et al.*, 2021)	*Centella* triterpenes (asiaticoside, madecassoside, asiatic acid)	Synaptic plasticity + metabolic regulation	5xFAD AD mice (500 mg/kg)	↑ synaptic protein expression; normalization of purine and nicotinate metabolic pathways (P<0.05)	Improved neuronal metabolic and synaptic integrity; ↑ memory performance	Amelioration of AD-related cognitive impairment
Gray et al., 2018 (Nora E. Gray *et al.*, 2018)	*Centella asiatica* water extract	NRF2-mediated antioxidant defence + synaptic plasticity	Mouse (NRF2 signalling)	↑ NRF2 expression; ↑ antioxidant response genes; ↑ synaptophysin & porin; ↑ hippocampal spine density (~20%, P<0.01)	Enhanced synaptic connectivity and oxidative resilience	Improved learning via structural plasticity
Brickman et al., 2014 (Brickman *et al.*, 2014)	Cocoa flavanols	Neurovascular coupling + hippocampal neurogenesis	Mouse + human DG model (900 mg/day, 3 months)	↑ dentate gyrus capillary density; ↑ neurogenesis; ↑ DG activation	Faster recognition memory (−630 ms vs control; P=0.038; Cohen's d≈0.82)	Enhanced hippocampal-dependent memory
Stringer et al., 2015 (Stringer, Guerrieri and Van Praag, 2015)	Epicatechin	BDNF–CREB signaling + monoaminergic modulation	Mouse neuronal model (0.5 mg/mL, 2 weeks)	pro-BDNF ↑ 1.74-fold (t(11)=2.58, P<0.03); mature BDNF ↑ 1.34-fold (t(12)=2.19, P<0.05); CREB phosphorylation: hippocampus ↑ 1.47-fold (P<0.05), cortex ↑ 2.33-fold (P<0.02); total hippocampal BDNF ≈ +35%; serotonin ↑ 23% (P<0.05)	Enhanced synaptic signaling; reduced anxiety-like behaviour in aged mice	Memory enhancement via neurotrophic and serotonergic potentiation
Carballeda Sangiao et al., 2021 (Carballeda Sangiao *et al.*, 2021)	Cocoa flavonoids	Oxidative stress modulation	SH-SY5Y neuronal cells	↓ ROS; ↑ antioxidant enzyme activity; GSH restoration: partial at 100 µg/mL cocoa or 1 µM epicatechin; complete at 200 µg/mL cocoa or 10 µM epicatechin	Dose-dependent cellular antioxidant protection	Prevents oxidative stress–induced cognitive decline
Lamport et al., 2020 (Lamport, Christodoulou and Achilleos, 2020b)	Dark chocolate (70%, ~83 mg flavonoids)	Acute neurovascular response	Human (35 g; acute 2 h; young adults)	↑ cerebral perfusion (inferred mechanism); improved verbal episodic memory vs white chocolate (P<0.05–0.01); no dose–response gradient reported	Rapid neurovascular-mediated cognitive enhancement	Acute episodic memory improvement via blood-flow modulation
Ricardi et al., 2025 (Ricardi *et al.*, 2025)	β-Caryophyllene	CB2R / NF-κB signalling	AD models + hippocampal slices	Restored LTP; ↑ BDNF; ↑ SIRT1; ↑ PGC-1α; ↓ TNF-α, ↓ IL-6 via NF-κB inhibition; reversal of Aβ-induced synaptic deficits	Synaptic recovery and reduced neuroinflammation	Reversal of neurodegenerative cognitive impairment
Lopes Mesquita et al., 2019 (Lopes Mesquita *et al.*, 2019)	β-Caryophyllene	Immune modulation (Th1/Th17 shift)	EAE mouse model (25–50 mg/kg)	↓ IL-17 across brain regions; ↓ T-bet; ↑ GATA-3; significant remyelination; improved myelin damage scores	Reduced CNS inflammation and demyelination	Indirect cognitive preservation via white matter integrity

Abbreviations: *Aβ, amyloid-beta; BDNF, brain-derived neurotrophic factor; CB2R, cannabinoid receptor type-2; COX-2, cyclooxygenase-2; CREB, cAMP response element-binding protein; DG, dentate gyrus; GATA-3, GATA-binding protein 3; GSH, glutathione; IL-6, interleukin-6; IL-17, interleukin-17; LTP, long-term potentiation; NF-κB, nuclear factor-κB; NRF2, nuclear factor erythroid 2–related factor 2; NSCs, neural stem cells; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; SIRT1, sirtuin 1; T-bet, T-box transcription factor TBX21; TNF-α, tumor necrosis factor-α.*

Table 3. Cognitive domain × intervention outcome matrix — direction and consistency of effects across included clinical trials.

Cognitive domain	*Bacopa monnieri*	*Centella asiatica*	Cocoa flavanols	β-Caryophyllene	Combined formulations
Working memory (WM)	✓ Consistent ↑ (Stough 2008; Peth-Nui 2012; Kumar 2016)	— Limited data	✓ Acute ↑ (Field 2011)	—	—
Episodic / verbal memory	✓ Consistent ↑ across 5 RCTs (Morgan 2010; Calabrese 2008; Raghav 2006; Peth-Nui 2012; Stough 2008)	✓ ↑ (Fitriana 2021; Lamport 2020 [cocoa])	✓ Acute episodic ↑ (Lamport 2020)	✓ ↑ vs baseline (Bauer 2021)	✓ ↑ (Cicero 2017)
Attention / processing speed	✓ ↑ attention speed & continuity (Peth-Nui 2012; Kumar 2016)	✓ ↓ reaction time at 750 mg (Wattanathorn 2008)	✓ ↑ RT accuracy (acute) (Field 2011)	—	—
Executive function (TMT, Stroop, fluency)	✓ ↑ multiple RCTs (Crosta 2020; Calabrese 2008; Raghav 2006)	— Limited data	✓ ↑ strong dose-dependent effect (Mastroiacovo 2014; Desideri 2012) □ Null (Suominen 2020)	—	—
Global cognition (MMSE/MoCA)	✓ ↑ (Cicero 2017)	—	□ Null (Baker 2022 COSMOS, 3 yr)	—	✓ ↑ (Cicero 2017 combination)
Subjective cognitive complaints	✓ ↓ CFQ subscales 27–36% (Bauer 2021 BCP); ↓ stress (Benson 2014)	—	—	✓ ↓ 27–36% CFQ (Bauer 2021)	✓ ↓ stress (Cicero 2017)
Mood / stress	✓ ↓ cortisol (Benson 2014); ↓ CESD (Calabrese 2008)	Trend ↑ mood (Wattanathorn 2008, NS)	—	—	✓ ↓ PSQ, SRDS (Cicero 2017)

Abbreviations: *✓ = positive effect observed in ≥1 included RCT; □ = null result; — = no eligible studies; ↑ = improvement; ↓ = reduction (favourable direction). Evidence quality refers to overall confidence based on number of studies, RoB rating, and consistency of findings. WM = working memory; CFQ = Cognitive Failures Questionnaire; MMSE = Mini-Mental State Examination; TMT = Trail Making Test; PSQ = Perceived Stress Questionnaire; SRDS = Self-Rating Depression Scale; CESD = Center for Epidemiologic Studies Depression Scale; RCT = randomized controlled trial.*

Table 4. Neurobiological mechanism summary - bioactive compounds and implicated pathways (clinical and preclinical evidence combined).

Neurobiological mechanism	*Bacopa monnieri*	*Centella asiatica*	Cocoa flavanols / Epicatechin	β-Caryophyllene	Supporting references
Cholinergic modulation (↓ AChE)	✓	—	—	—	Peth-Nui et al., 2012
Neurotrophic signaling (↑ BDNF)	✓ (preclinical)	✓	✓	✓	Ar Rochmah 2019; Stringer 2015; Ricardi 2025
Antioxidant defence (↑ NRF2, SOD, GSH)	✓	✓	✓	—	Gray 2018; Carballeda Sangiao 2021; Fitriana 2021
Anti-neuroinflammation (↓ TNF-α, IL-6, NF-κB)	✓	✓	—	✓	Nemetchek 2016; Ar Rochmah 2019; Ricardi 2025; Kobaek-Larsen 2019
Synaptic plasticity (↑ synaptophysin, LTP)	✓ (preclinical)	✓	✓	✓	Gray 2018; Speers 2021; Stringer 2015; Ricardi 2025
Hippocampal neurogenesis	—	—	✓	—	Brickman et al., 2014
Neural stem cell proliferation	—	—	—	—	Hucklenbroich et al., 2014
Cerebrovascular / neurovascular coupling	—	—	✓	—	Brickman 2014; Lamport 2020
HPA-axis / cortisol modulation	✓	—	—	—	Benson et al., 2014
CB2 receptor / endocannabinoid tone	—	—	—	✓	Ricardi 2025; Swindell 2022
Metabolic regulation (purine, nicotinate pathways)	—	✓	—	—	Speers et al., 2021
Remyelination / white matter integrity	—	—	—	✓	Lopes Mesquita et al., 2019

Abbreviations: *✓ = evidence of pathway involvement from ≥1 included study (clinical or preclinical); — = no evidence found in included studies. Green shading denotes documented mechanistic activity. AChE = acetylcholinesterase; BDNF = brain-derived neurotrophic factor; CB2 = cannabinoid receptor type 2; GSH = glutathione; HPA = hypothalamic–pituitary–adrenal; LTP = long-term potentiation; NF-κB = nuclear factor kappa B; NRF2 = nuclear factor erythroid 2-related factor 2; SOD = superoxide dismutase; TNF-α = tumor necrosis factor-α.*

Discussion

The present systematic review brings together 17 randomized controlled human trials and 13 mechanistic evidence evaluating bioactive ingredients commonly found in the herbal chocolate formulations combining *Bacopa monnieri* and *Centella asiatica,* such as commercially available 'Memory melt chocolate'. Collectively, the data suggest that these ingredients interact with multiple neurobiological pathways relevant to cognition. However, the strength and consistency of clinical evidence differ substantially between compounds and across cognitive domains.

Overall, cocoa flavanols have consistently improved tasks involving processing speed and executive control in small trials, whereas *Bacopa* has most reliably enhanced memory performance in longer-term studies. By contrast, controlled trials of *Centella asiatica* have not demonstrated clear cognitive benefits beyond modest improvements in alertness (Puttarak *et al.*, 2017). Findings likely reflect both genuine differences in bioactivity and heterogeneity in study designs (e.g. sample size, dose and duration), such that null results have occurred when dosing, baseline cognition, or outcome timing were suboptimal (Kongkeaw *et al.*, 2014; Baker *et al.*, 2022)

Across trials, cocoa flavanols demonstrated the most consistent domain-specific effects, particularly in executive processing speed, attention, and task switching. Improvements in Trail Making performance and verbal fluency reported in elderly cohorts align with experimental evidence that flavanol intake enhances regional cerebral perfusion and oxygenation, mechanisms believed to support neuronal efficiency and synaptic activity. Human imaging studies show that high-flavanol cocoa acutely increases regional cerebral blood flow, particularly in frontal and cingulate areas implicated in executive control, supporting a mechanistic basis for observed cognitive improvements.

However, the large long-term COSMOS-Mind trial showing no overall effect on global cognition suggests that flavanol benefits may be conditional rather than universal. The divergence between short-term task improvements and null long-term global cognition outcomes suggests that flavanol effects may be context-dependent. Rather than modifying long-term neurodegenerative trajectories, flavanols may enhance cognitive efficiency, vascular responsiveness, or resilience under specific testing conditions.

In the following sections we examine evidence for each ingredient by cognitive domain, integrate mechanistic insights, and highlight factors influencing mixed outcomes.

Domain-specific effects of herbal chocolate components

Cocoa flavanols

Preclinical and clinical data shows improved neurovascular function as a key mechanism for flavanol-rich cocoa beverages. Epicatechin and related flavanols enhance cerebral blood flow, cross the blood–brain barrier, and activate neurotrophic signaling and slow down cognitive decline (Baker *et al.*, 2022). In addition to vascular modulation, experimental evidence demonstrates that epicatechin directly upregulates hippocampal brain-derived neurotrophic factor (BDNF) (pro-BDNF ↑1.74-fold; mature BDNF ↑1.35-fold) and increases CREB phosphorylation in both hippocampal and cortical regions ($P<0.05$), indicating activation of synaptic plasticity pathways underlying learning and memory processes (Stringer, Guerrieri and Van Praag, 2015).

These vascular and neurotrophic actions provide a biologically coherent basis for potential cognitive effects. In acute and short-term trials of healthy or at-risk older adults (typically 8–12 weeks), high-flavanol cocoa (993 mg/day) reliably sped task performance on the Trail-Making Test (processing speed) and increased verbal fluency or other executive measures relative to low-flavanol controls (Mastroiacovo *et al.*, 2014; Daniel J. Lamport *et al.*, 2015). 8 weeks of daily high-flavanol cocoa (993 mg) significantly reduced Trails A and B completion times and produced greater category fluency gains relative to a low-flavanol beverage (Mastroiacovo *et al.*, 2014). These findings are further supported by dose–response data from elderly populations with mild cognitive impairment, where high (≈990 mg/day) and intermediate (≈520 mg/day) flavanol intake significantly improved executive function and processing speed alongside reductions in insulin resistance markers, reinforcing a coupled metabolic–cognitive response (Desideri *et al.*, 2012).

Similarly, a cross-over MRI study reported that a single dose of high-flavanol cocoa markedly increased resting blood flow in the anterior cingulate and parietal cortex of older adults (Daniel J Lamport *et al.*, 2015), brain regions critical for attention and executive control. Acute intervention studies further demonstrate that flavanol-rich dark chocolate (720 mg) can improve spatial working memory, processing speed, and reduce mental fatigue within 1–2 hours post-consumption ($P<0.05$), indicating rapid neurovascular-mediated cognitive effects (Field, Williams and Butler, 2011). Consistent with this, acute intake of 70% dark chocolate (35 g with a total flavonoid content 83 mg) significantly enhanced verbal episodic memory performance compared to white chocolate controls within 2 hours ($P<0.05$), further supporting a rapid perfusion-driven mechanism (Lamport, Christodoulou and Achilleos, 2020a). These regional perfusion effects suggest an acute mechanism by which flavanols facilitate neuronal function.

Notably, human trials have repeatedly observed that cognitive tests of executive function and processing speed are particularly sensitive to cocoa flavanols, whereas effects on memory are less consistently captured (Daniel J Lamport *et al.*, 2015). Higher flavanol doses (approximately 500–750 mg/day) preferentially benefit executive and processing domains, with weaker or more variable effects on episodic memory (Daniel J. Lamport *et al.*, 2015; Baker *et al.*, 2022). However, emerging evidence indicates that hippocampal-dependent memory may be selectively enhanced under specific conditions, as high-

flavanol intake has been associated with increased dentate gyrus activation and capillary density, linking vascular remodeling to improved memory task performance (Brickman *et al.*, 2014).

Additional RCTs support these findings. A three-month trial of 900 mg/d versus 45 mg/d flavanols showed increased dentate gyrus blood flow and concurrent improvement on a hippocampal-dependent memory task in middle-aged adults (Baker *et al.*, 2022). Likewise, the CoCoA trial (Desideri et al.) found that both high (993 mg) and intermediate (520 mg) flavanol beverages enhanced composite executive-function scores relative to a very low-flavanol control (Baker *et al.*, 2022). These cognitive benefits in small trials were paralleled by metabolic changes (improved insulin sensitivity and reduced oxidative stress) (Mastroiacovo *et al.*, 2014), consistent with a vasculo-metabolic mechanism. At the cellular level, cocoa flavonoids have also been shown to significantly reduce reactive oxygen species (ROS) production and enhance endogenous antioxidant enzyme activity in neuronal models, indicating an additional layer of neuroprotection against oxidative stress–mediated cognitive decline (Carballeda Sangiao *et al.*, 2021). Collectively, these studies indicate that flavanols can acutely enhance processing speed and higher-order cognition, likely via vascular, antioxidant, and neurotrophic pathways.

However, the larger and longer-term evidence is less definitive. The COSMOS-Mind trial, which followed 2,262 older adults over three years, found no significant effect of 500 mg/day flavanols on global cognitive scores (Baker *et al.*, 2022). Similarly, the FlaSeCo randomized controlled trial (410 mg/day vs 86 mg/day for 8 weeks) reported no significant differences between groups in TMT-A (P=0.93), TMT-B (P=0.66), or verbal fluency outcomes, suggesting that moderate flavanol doses or high baseline cognitive status may attenuate detectable effects (Suominen *et al.*, 2020). This apparent discrepancy warrants careful interpretation rather than dismissal. Critically, COSMOS-Mind measured cognition only annually and included theobromine/caffeine in the supplement, potentially diluting pure flavanol effects. The absence of benefit might also reflect insufficient dose or missed short-term effects (Baker *et al.*, 2022). Moreover, secondary analyses and prior trials suggest a dose–response pattern, raising the possibility that 500 mg/day was insufficient to reproduce the executive benefits observed at higher doses (Baker *et al.*, 2022). Thus, apparent discrepancies (small positive trials vs. a large null trial) likely stem from differences in study design (duration, dosing, testing frequency) rather than a true contradiction. In summary, the smaller mechanistic RCTs consistently indicate that flavanols can enhance processing speed and executive performance, plausibly via vascular, antioxidant, and neurotrophic pathways. In contrast, large-scale prevention trials have yet to demonstrate durable global cognitive effects. This divergence likely reflects differences in design, duration, and outcome sensitivity rather than a simple contradiction in efficacy, underscoring the need for more targeted, well-powered studies.

Bacopa monnieri

In contrast to cocoa, *Bacopa monnieri* trials consistently show improvements in memory acquisition, delayed recall, and working memory accuracy across multiple RCTs. Mechanistic evidence supports a multimodal pathway including acetylcholinesterase inhibition, anti-inflammatory activity, and enhancement of synaptic signaling. Human plasma studies showing reduced AChE activity after supplementation provide translational support for a cholinergic mechanism underlying memory enhancement. In addition, controlled trials in healthy elderly populations demonstrate that *Bacopa* (300–600 mg/day over 12 weeks) significantly improves “quality of memory” and “continuity of attention” (P<0.001), with measurable increases in attention speed emerging by weeks 8–12 (P<0.01), suggesting progressive neurocognitive adaptation rather than acute effects (Peth-Nui *et al.*, 2012).

The most robust RCT findings are for verbal learning and recall. For example, a 12-week trial in older adults found that 300 mg/d of standardized *Bacopa* extract (BacoMind™) significantly improved AVLT measures of verbal learning and delayed recall versus placebo (Morgan and Stevens, 2010). An earlier 12-week study likewise showed that *Bacopa* significantly enhanced delayed word recall on the Rey Auditory Verbal Learning Test compared to placebo, and also improved performance on the Stroop test of attention/inhibition (Calabrese *et al.*, 2008). These findings are supported by additional randomized trials demonstrating improvements in spatial working memory accuracy following 90 days of *Bacopa* supplementation (300 mg/day) in healthy adults (P<0.05), indicating that both verbal and visuospatial memory domains are responsive to intervention (Stough *et al.*, 2008). Similarly, a trial in elderly individuals with age-associated cognitive decline report significant improvements in mental control, logical memory, and paired-associate learning after 12 weeks of *Bacopa* administration (P<0.05), further reinforcing its effects across multiple hippocampal-dependent memory systems (Raghav, Singh, P. Dalal, *et al.*, 2006b).

These findings align with systematic reviews: Pase et al. reported that most *Bacopa* trials (300–450 mg/day over ≥12 weeks) found gains on free recall memory tasks, whereas effects in other domains were less consistent (Pase *et al.*, 2012). A meta-analysis of nine RCTs similarly concluded that *Bacopa* extract significantly reduced choice reaction time and improved Trail-Making Test B (attention/processing) (Kongkeaw *et al.*, 2014). Recent controlled trials further extend these observations into executive domains, where *Bacopa*-containing antioxidant combinations have demonstrated substantial reductions in TMT-B completion time (−21.0 seconds vs placebo, P<0.0001), alongside improvements in TMT-A and verbal fluency performance, indicating enhanced executive flexibility and processing speed (Crosta et al., 2020). Similarly, multi-component *Bacopa*-based nutraceutical formulations have shown improvements in global cognition (MMSE, P<0.05) and reductions in perceived stress indices (PSQ, P<0.05), suggesting broader cognitive and affective benefits (Cicero *et al.*, 2017). Thus, like cocoa, *Bacopa* appears to sharpen processing speed/attention, but its effects on episodic memory (learning and recall) have been more prominent.

In contrast to these positive findings, a few trials have reported no cognitive benefit. Small sample sizes and short durations are often implicated. For example, one 12-week study (30 subjects) of 450 mg *Bacopa* showed no significant change on memory or processing tests (though anxiety trended downward) (*Bacopa monnieri - StatPearls - NCBI Bookshelf*, no date; Sathyanarayanan *et al.*, 2013). This null finding may reflect insufficient power or insensitivity of the tests. Indeed, the meta-analysis noted that variability in cognitive outcomes across *Bacopa* studies likely arises from inconsistent measurement and sample characteristics (Pase *et al.*, 2012). However, emerging evidence suggests that *Bacopa* may exert context-dependent effects, as acute administration under stress conditions has been shown to significantly improve cognitive performance (Stroop, mental arithmetic) while simultaneously reducing cortisol responses (P<0.05), indicating a stress-buffering mechanism that may not be captured in resting-state cognitive paradigms (Benson *et al.*, 2014).

Overall, the evidence strength for *Bacopa* is moderate: multiple well-designed trials report positive memory effects, but sample sizes (often 50–100) are relatively small and formulations vary. Nonetheless, the pattern of results is convergent enough that a meta-review concluded *Bacopa* improves "speed of attention" and reaction time (Kongkeaw *et al.*, 2014), and systematic reviewers highlight its memory gains (Pase *et al.*, 2012). Additional controlled trials in specific populations, such as medical students, further demonstrate significant improvements in working memory, logical memory, and reduced distractibility within as early as 6 weeks of supplementation ($P<0.05$), suggesting that cognitive enhancement may also extend to high-demand cognitive environments (Kumar *et al.*, 2016).

Mechanistically, *Bacopa* influences cholinergic and neurotrophic systems. *In vitro* studies show that *Bacopa* extracts inhibit acetylcholinesterase and upregulate hippocampal muscarinic receptor expression, increasing acetylcholine signaling (Pandareesh and Anand, 2013). Simultaneously, *Bacopa* activates neurotrophic pathways: it markedly elevates BDNF levels and other plasticity markers in neuronal cultures (Pandareesh and Anand, 2013). In one PC12 cell model, *Bacopa* pretreatment (100 µg/mL) protected against scopolamine toxicity by downregulating AChE and upregulating BDNF and M1 muscarinic receptors, along with restoring antioxidant enzyme activity (Pandareesh and Anand, 2013). Animal studies corroborate these actions, showing that *Bacopa* extracts reduce oxidative stress and inflammation, normalize cholinergic deficits, and enhance synaptic proteins, which together could underlie improvements in learning and memory. In addition, bacoside-rich extracts have been shown to directly suppress neuroinflammatory pathways in activated microglial models, significantly reducing nitric oxide, TNF-α, and IL-6 production ($P<0.05$), indicating a direct anti-inflammatory mechanism at the level of central immune signaling (Nemetchek *et al.*, 2016).

The timeline of clinical effects (requiring weeks of supplementation) is consistent with these cellular changes accumulating over time. Thus, *Bacopa* likely exerts memory-enhancing effects via cholinergic modulation, neuroprotection, and increased synaptic plasticity.

Centella asiatica

Despite historical use as a "brain tonic," human trials of *Centella asiatica* have yielded mixed cognitive results. A 2017 systematic review/meta-analysis of five placebo-controlled RCTs of *C. asiatica* (alone) and six RCTs of *C. asiatica*-containing products (in mixtures) found no significant benefit in any cognitive domain (memory, attention, executive function) (Puttarak *et al.*, 2017). The only consistent signal was modest improvement in subjective alertness and reduced anger scores, rather than objective memory gain (Puttarak *et al.*, 2017). To our knowledge, no large RCT has tested high-dose standardized *Centella* for memory or attention outcomes. Thus, as of now the clinical evidence does not support a cognitive-enhancing effect in humans. However, earlier randomized and controlled human studies suggest subtle cognitive and mood-related improvements under specific conditions. For example, administration of *Centella asiatica* extract (250–750 mg/day for 2 months) in older adults showed a trend toward improved working memory and mood scores, although effects were modest and not statistically robust (Wattanathorn *et al.*, 2008). Similarly, a randomized controlled trial in women with dementia reported that *Centella* (250–750 mg/day for 12 weeks) significantly improved memory performance ($P=0.001$) and increased antioxidant enzyme activity (SOD; $P=0.009$), with further enhancement when combined with aerobic exercise (Anisa Fitriana *et al.*, 2021). These findings suggest that cognitive benefits may emerge in impaired populations or under oxidative-stress–related conditions rather than in healthy individuals.

However, *Centella* may improve cognition in vulnerable states or through indirect pathways. The same Puttarak *et al.* 2017, review noted heterogeneity in extract types and doses; some individual studies in neurological conditions suggested better working memory, though not robustly (Puttarak *et al.*, 2017). Importantly, animal and cellular studies give a good mechanistic picture: *Centella*'s triterpenes (asiaticoside, madecassoside, asiatic acid) have antioxidant, anti-inflammatory, and neurotrophic actions (Khairinisa, Fakih and Ramadhan, 2025). For example, Asiaticoside treatment in aged or ischemic rodents upregulates hippocampal signaling - specifically PKA and CaMKII - and increases synaptic plasticity proteins like synaptophysin and PSD-95 (Nora E Gray, Zweig, *et al.*, 2018). Madecassoside similarly alleviates chemically-induced cognitive deficits by inhibiting p38 MAPK and reducing inflammatory cytokines (Lin *et al.*, 2014). Furthermore, asiatic acid has been shown to boost hippocampal neurogenesis and reduce reactive oxygen species by activating Nrf2-mediated antioxidant genes (Gray *et al.*, 2017). Several *Centella* constituents also inhibit acetylcholinesterase and attenuate amyloid toxicity *in vitro* (Gray *et al.*, 2017; Puttarak *et al.*, 2017). Additional mechanistic evidence strengthens these observations: chronic administration of *Centella asiatica* in stressed rats significantly reduced hippocampal TNF-α while increasing BDNF levels, indicating simultaneous anti-inflammatory and neurotrophic effects relevant to cognition (Ar Rochmah *et al.*, 2019). In Alzheimer's disease 5xFAD mouse models, *Centella* triterpenes improved memory performance and increased synaptic protein expression, thereby supporting enhanced synaptic plasticity pathways (Speers *et al.*, 2021). Moreover, water extracts of *Centella asiatica* activated NRF2-mediated antioxidant signaling and increased synaptic density , such as synaptophysin and porin, in hippocampal tissue, thereby antioxidant defense to improved cognitive function (Nora E Gray, Alcazar Magana, *et al.*, 2018). These findings plausibly explain why *Centella* has demonstrated anxiolytic and neuroprotective effects in animals. Yet the lack of clear clinical efficacy may reflect differences in dosing or preparation: traditional use (fresh leaf smoothies, water extracts) may not match the standardized extracts used in trials (Puttarak *et al.*, 2017). It is also possible that *Centella* benefits cognition only in populations with impairment or high stress, a hypothesis that awaits testing.

Although experimental studies demonstrate strong neuroprotective potential for *Centella asiatica*, human trials have yielded mixed results (Teerapattarakan *et al.*, 2025).These inconsistencies may reflect the inherent challenges in conducting large-scale, well-funded trials for nutraceuticals compared to the heavily supported pharmaceutical sector. However, the lack of adverse effects and the historical safety profile of these herbs support their continued exploration as cost-effective alternatives for cognitive health (Puttarak *et al.*, 2017; Wong, Barron and Abdullah, 2021).

Combined and synergistic effects

While individual ingredients show some promise, the medicinal chocolate strategy under review combines them, aiming for additive or synergistic action. Conceptually, cocoa flavanols and *Centella* emphasize vascular and antioxidant pathways, whereas *Bacopa* emphasizes cholinergic and synaptic plasticity.

Thus, the multi-ingredient formulation covers a broad therapeutic spectrum: e.g. acute enhancement of cerebral perfusion by flavanols could support the slower synaptic improvements driven by *Bacopa*'s neuromodulation, while *Centella*'s antioxidant/anti-inflammatory effects may protect against neurodegenerative processes. Although no clinical trial has yet evaluated this specific combination, some controlled trials have used similar pairings: for instance, Ayurvedic practices combine *Bacopa* with Gotu kola (*Centella*) for synergistic cognitive and mood support. (*Bacopa monnieri - StatPearls - NCBI Bookshelf*, no date). Theoretically, such synergy could manifest in greater effects on memory and processing than either component alone. However, potential interactions (e.g. all three together) are untested, and the formulation's efficacy will depend on achieving active doses of each compound. It is also critical to standardize active ingredients (flavanol content, bacoside content, triterpene levels), since variability in composition could undermine reproducibility.

Strength and consistency of evidence

Across compounds, the majority of RCTs are relatively small (tens to low hundreds of subjects) and of short-to-medium duration (weeks to a few months) (Kongkeaw *et al.*, 2014; Baker *et al.*, 2022). Such studies can detect moderate effects on specific cognitive tests but may be underpowered to detect small global changes or to systematically explore dose–response. For cocoa flavanols and *Bacopa*, multiple RCTs and meta-analyses (though few with >100 participants) provide convergent evidence in targeted domains (Calabrese *et al.*, 2008; Kongkeaw *et al.*, 2014; Mastroiacovo *et al.*, 2014).

Key limitations affect confidence in the evidence. Many RCTs use different cognitive domains and outcome definitions, making cross-study comparison difficult. Small samples inflate the risk of both type I (false positives) and type II (false negatives) errors. For example, *Bacopa* meta-analyses noted that Trails and reaction-time improvements (on the order of 10–20 ms) were statistically significant (Kongkeaw *et al.*, 2014), but such small changes might not replicate in underpowered trials. Similarly, cocoa studies often examine intermediate outcomes (e.g. TMT performance or brain activation) rather than long-term memory. The null COSMOS-Mind trial (Baker *et al.*, 2022), illustrates how even a large study can miss acute effects if the testing schedule is sparse and dose modest (Baker *et al.*, 2022).

Null findings and heterogeneity

Null results in some RCTs can stem from several factors. Insufficient dosing is a recurring concern: Bacopa often requires chronic administration (≥12 weeks) to show effects, and under-dosing (<300 mg/d or short duration) may yield no change. In COSMOS-Mind, the 500 mg flavanol dose was lower than in positive trials, and cognitive testing only at yearly intervals would not capture transient benefits. Participant selection also matters: many subjects in these trials are cognitively healthy or only mildly at-risk, creating a ceiling effect that limits detectable improvement. Conversely, interventions might have larger effects in those with low baseline function or vascular impairment. Indeed, an Australian subgroup analysis found greater cognitive gain in Bacopa-treated individuals with poorer baseline memory. Genetic and lifestyle differences could further modulate response. Lastly, publication bias favoring positive studies is a concern in nutraceutical research, as smaller negative trials may be less likely to be reported trials may be less likely to be reported.

Mechanisms of action

The evidence suggests several interconnected neurobiological pathways through which these ingredients may support cognition. Cocoa flavanols enhance endothelial function and cerebral blood flow (Daniel J. Lamport *et al.*, 2015; Baker *et al.*, 2022), thereby improving neuronal energy delivery and metabolic waste clearance, which is particularly relevant for attention and executive processes. Concurrently, all three ingredients exhibit antioxidant and anti-inflammatory properties; preclinical studies indicate that cocoa and *Centella asiatica* activate the Nrf2 pathway to mitigate oxidative stress (Gray *et al.*, 2017). Both flavanols and Centella suppress pro-inflammatory signaling cascades, including 5-lipoxygenase and p38 MAPK pathways. Bacopa monnieri exerts a more direct effect on cholinergic neurotransmission, with randomized controlled trials demonstrating memory improvements consistent with enhanced cholinergic tone, supported mechanistically by reduced acetylcholinesterase activity and increased muscarinic receptor expression (Pandareesh and Anand, 2013). In parallel, *Centella*-derived triterpenes have shown in vitro acetylcholinesterase inhibitory activity (Puttarak *et al.*, 2017), suggesting complementary cholinergic modulation. At the level of synaptic plasticity, both *Bacopa* and *Centella* upregulate neurotrophic factors and synaptic proteins; *Bacopa* increases brain-derived neurotrophic factor (BDNF) and antioxidant enzymes, while *Centella* enhances synaptophysin, PSD-95, and neurogenic signaling within the hippocampus (Pandareesh and Anand, 2013) , collectively supporting synaptic strengthening and long-term learning. Additionally, stress modulation appears to be a contributory mechanism, as *Bacopa* demonstrates anxiolytic effects, including reductions in cortisol and anxiety in clinical trials (Calabrese *et al.*, 2008), and *Centella*'s adaptogenic properties may further mitigate stress-induced cognitive impairment. Taken together, these multi-targeted mechanisms provide a coherent rationale for combination formulations; for instance, cocoa flavanol-mediated improvements in insulin sensitivity (Mastroiacovo *et al.*, 2014) may synergize with *Bacopa*'s cholinergic enhancement to facilitate memory encoding. However, this mechanistic convergence also introduces complexity, as suboptimal dosing or pathway saturation could lead to diminished or non-additive effects, underscoring the need for carefully controlled combinatorial studies.

Clinical and translational implications

The findings suggest that medicinal chocolate products could serve as adjunctive cognitive support interventions, particularly for aging populations or individuals with early vascular or metabolic decline. Their potential advantages include high acceptability, ease of delivery, and compatibility with long-term use compared with pharmacological cognitive enhancers.

However, current evidence does not support medicinal chocolate as a treatment for established cognitive impairment or neurodegenerative disease. Instead, its strongest potential role lies in cognitive maintenance, stress resilience, and prevention of vascular-linked cognitive decline.

Limitations

The available literature is constrained by several limitations that restrict firm conclusions regarding efficacy. As noted in the current funding landscape, support for large-scale clinical trials involving natural products is often limited compared to the pharmaceutical sector. Consequently, many trials are relatively small and therefore statistically not strong to detect modest cognitive effects, increasing the risk of false-negative or inflated positive findings. Considerable heterogeneity also exists in ingredient combinations, with studies testing different multi-component formulations, making cross-trial comparisons difficult. In addition, standardization is inconsistent, particularly for cocoa flavanol dose and *Bacopa monnieri* extract composition, both of which strongly influence bioactivity and reproducibility. Some preclinical work has examined formulations combining *Bacopa monnieri* and *Centella asiatica* (such as Medhya rasayana) suggesting potential synergistic effects on neuroinflammation and cognition in animal models, and at least one recent randomized controlled trial in children has compared the effects of both the extracts separately, but high-quality clinical evidence for a defined 1:1 ratio or optimized extract combination in humans remains limited and not yet conclusive. However, it is important to contextualize these findings within the framework of traditional medicine; unlike modern pharmaceuticals that often carry significant side effects, these natural ingredients have been utilized for centuries with a high degree of safety (Orhan, 2012). Long-term outcomes relevant to neurodegeneration, cognitive decline trajectories, or prevention of dementia remain insufficiently studied, as most interventions are short in duration. Finally, the nutraceutical field is susceptible to publication bias favoring positive results, which may overestimate true clinical effectiveness. Collectively, these limitations reduce confidence in defining optimal formulations or making definitive claims about long-term cognitive benefit.

Future directions

Future trials should prioritize standardized flavanol dosing, longer intervention periods, and multimodal outcome measures that integrate cognitive testing with neuroimaging or vascular biomarkers. Studies directly evaluating combined cocoa–herbal formulations are particularly needed; as current trials largely assess single ingredients despite commercial products containing complex mixtures. Furthermore, research should focus on the role of these ingredients as safe, cost-effective nutraceuticals. Investigating their broader health benefits, such as cardiovascular support and stress reduction, would provide a more holistic understanding of their value beyond isolated cognitive metrics.

Conclusion

This systematic review suggests that combining Bacopa monnieri and Centella asiatica in a cocoa-based delivery system, such as the commercially available ‘Memory melt chocolate,’ may offer cognitive benefits, especially for executive function, processing speed, and memory. Randomized controlled trials indicate that cocoa flavanols may primarily support cognition through vascular and metabolic pathways, potentially leading to short- to medium-term improvements in at-risk populations. Botanical ingredients such as Bacopa monnieri, on the other hand, seem to act more gradually and may influence synaptic plasticity, cholinergic signaling, and stress regulation. Together, the combination of vascular, anti-inflammatory, antioxidant, and neurotrophic effects provide a reasonable mechanistic basis for using multi-ingredient chocolate as a functional cognitive intervention.

Centella asiatica shows strong preclinical promise (antioxidant, neurotrophic effects) but variable results in RCTs, its value is reinforced by centuries of traditional Ayurvedic use as a safe 'brain tonic'. This long-standing experience offers a valuable perspective, especially when compared to approved pharmaceuticals for dementia which, despite heavy investment, often yield only modest clinical benefits and significant side effects.

At the same time, the current evidence is varied and limited, making it difficult to establish clear guidance on dosing, formulation, or clinical use. Notably, none of the large RCTs tested the combined formulation, so its actual combined efficacy remains speculative. Key gaps include standardization of dosages, longer follow-up (for example, to detect sustained or preventive effects), and RCT trials focusing on all the specific domains most likely to respond. Incorporating neuroimaging or physiological biomarkers (CBF, endothelial function, BDNF levels) could clarify mechanisms and identify subgroups who benefit. Addressing these gaps will give a full picture of this medicinal coco-based delivery system combining *Bacopa monnieri* and *Centella asiatica*.

Declarations

Acknowledgements

The authors thoroughly reviewed, revised, and approved of all content and took full responsibility for the scientific accuracy of the final version.

Disclosure statement

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

Additional information

Funding

This study was not supported by any external funding source and reflects the independent work and interests of the authors.

References

1. Alberti TB et al (2017) (−)-β-Caryophyllene, a CB2 Receptor-Selective Phytocannabinoid, Suppresses Motor Paralysis and Neuroinflammation in a Murine Model of Multiple Sclerosis, *International Journal of Molecular Sciences 2017, Vol. 18, Page 691*, 18(4), p. 691. Available at: https://doi.org/10.3390/ijms18040691
2. Anisa Fitriana L et al (2021) Effect of Centella Asiatica and Aerobic Exercise in Older Women With Dementia: A Randomized Controlled Trial. Malaysian J Med Health Sci 17(SUPP14):2636–9346
3. Ar Rochmah M et al (2019) Centella asiatica Prevents Increase of Hippocampal Tumor Necrosis Factor-α Independently of Its Effect on Brain-Derived Neurotrophic Factor in Rat Model of Chronic Stress, *BioMed Research International*, 2019(1), p. 2649281. Available at: https://doi.org/10.1155/2019/2649281
4. *Bacopa monnieri - StatPearls - NCBI Bookshelf* (no date). Available at: https://www.ncbi.nlm.nih.gov/books/NBK589635/ (Accessed: March 3, (2026)
5. Baker LD et al (2022) Effects of cocoa extract and a multivitamin on cognitive function: a randomized clinical trial, *Alzheimer's & dementia: the journal of the Alzheimer's Association*, 19(4), p. 1308. Available at: https://doi.org/10.1002/alz.12767
6. Benson S et al (2014) An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood, *Phytotherapy research: PTR*, 28(4), pp. 551–559. Available at: https://doi.org/10.1002/ptr.5029
7. Brickman AM et al (2014) Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults, *Nature Neuroscience 2014 17:12*, 17(12), pp. 1798–1803. Available at: https://doi.org/10.1038/nn.3850
8. Butterfield DA, Halliwell B (2019) Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease., *Nature reviews. Neuroscience*, 20(3), pp. 148–160. Available at: https://doi.org/10.1038/s41583-019-0132-6
9. Calabrese C et al (2008) Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: A randomized, double-blind, placebo-controlled trial, *Journal of Alternative and Complementary Medicine*, 14(6), pp. 707–713. Available at: https://doi.org/10.1089/acm.2008.0018
10. Carballeda Sangiao N et al (2021) Aqueous Extract of Cocoa Phenolic Compounds Protects Differentiated Neuroblastoma SH-SY5Y Cells from Oxidative Stress, *Biomolecules*, 11(9), p. 1266. Available at: https://doi.org/10.3390/biom11091266
11. Cicero AF et al (2017) Short-Term Impact of a Combined Nutraceutical on Cognitive Function, Perceived Stress and Depression in Young Elderly with Cognitive Impairment: A Pilot, Double-Blind, Randomized Clinical Trial, *The journal of prevention of Alzheimer's disease*, 4(1), pp. 12–15. Available at: https://doi.org/10.14283/jpad.2016.10
12. Crosta F et al (2020) Improvement of Executive Function after Short-Term Administration of an Antioxidants Mix Containing Bacopa, Lycopene, Astaxanthin and Vitamin B12: The BLAtwelve Study, *Nutrients*, 13(1), pp. 1–16. Available at: https://doi.org/10.3390/nu13010056
13. Desideri G et al (2012) Benefits in Cognitive Function, Blood Pressure, and Insulin Resistance Through Cocoa Flavanol Consumption in Elderly Subjects With Mild Cognitive Impairment, *Hypertension*, 60(3), pp. 794–801. Available at: https://doi.org/10.1161/HYPERTENSIONAHA.112.193060
14. Field DT, Williams CM, Butler LT (2011) Consumption of cocoa flavanols results in an acute improvement in visual and cognitive functions, *Physiology and Behavior*, 103(3–4), pp. 255–260. Available at: https://doi.org/10.1016/j.physbeh.2011.02.013
15. Gorelick PB et al (2011) Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association., *Stroke*, 42(9), pp. 2672–2713. Available at: https://doi.org/10.1161/STR.0b013e3182299496
16. Grassi D et al (2008) Blood Pressure Is Reduced and Insulin Sensitivity Increased in Glucose-Intolerant, Hypertensive Subjects after 15 Days of Consuming High-Polyphenol Dark Chocolate13, *The Journal of Nutrition*, 138(9), pp. 1671–1676. Available at: https://doi.org/10.1093/jn/138.9.1671
17. Gray NE et al (2017) Centella asiatica – Phytochemistry and mechanisms of neuroprotection and cognitive enhancement, *Phytochemistry reviews: proceedings of the Phytochemical Society of Europe*, 17(1), p. 161. Available at: https://doi.org/10.1007/s11101-017-9528-y
18. Gray NE, Alcazar Magana A et al (2018) Centella asiatica - Phytochemistry and mechanisms of neuroprotection and cognitive enhancement., *Phytochemistry reviews: proceedings of the Phytochemical Society of Europe*, 17(1), pp. 161–194. Available at: https://doi.org/10.1007/s11101-017-9528-y
19. Gray NE, Zweig JA et al (2018) Centella asiatica attenuates hippocampal mitochondrial dysfunction and improves memory and executive function in β-amyloid overexpressing mice., *Molecular and cellular neurosciences*, 93, pp. 1–9. Available at: https://doi.org/10.1016/j.mcn.2018.09.002
20. Gray NE et al (2018) Centella asiatica increases hippocampal synaptic density and improves memory and executive function in aged mice, *Brain and Behavior*, 8(7), p. e01024. Available at: https://doi.org/10.1002/brb3.1024
21. Hack W et al (2025) Triterpene and Caffeoylquinic Acid Constituents Contribute to the Cognitive-Enhancing, but Not Anxiolytic, Effects of a Water Extract of Centella asiatica in Aged Mice, *Nutrients*, p. 3171. Available at: https://doi.org/10.3390/nu17193171
22. Harada CN, Love N, M.C. and, Triebel KL (2013) Normal cognitive aging., *Clinics in geriatric medicine*, 29(4), pp. 737–752. Available at: https://doi.org/10.1016/j.cger.2013.07.002
23. Heneka MT et al (2015) Neuroinflammation in Alzheimer's disease., *The Lancet. Neurology*, 14(4), pp. 388–405. Available at: https://doi.org/10.1016/S1474-4422(15)70016-5

24. Iadecola C, Gottesman RF (2019) Neurovascular and Cognitive Dysfunction in Hypertension., *Circulation research*, 124(7), pp. 1025–1044. Available at: https://doi.org/10.1161/CIRCRESAHA.118.313260
25. Jiang J et al (2025) A review of neuroprotective properties of Centella asiatica (L.) Urb. and its therapeutic effects, *Annals of Medicine*, 57(1). Available at: https://doi.org/10.1080/07853890.2025.2559122
26. Khairinisa MA, Fakih TM, Ramadhan DSF (2025) Bioactive potential of Centella asiatica leaf extract in acetylcholinesterase (AChE) inhibition: Insights from multiple ligand mapping, *Computers in Biology and Medicine*, 197, p. 110970. Available at: https://doi.org/https://doi.org/10.1016/j.compbiomed.2025.110970
27. Kim JJ, Song EY, Kosten TA (2006) Stress effects in the hippocampus: Synaptic plasticity and memory, *Stress*, 9(1), pp. 1–11. Available at: https://doi.org/10.1080/10253890600678004
28. Kongkeaw C et al (2014) Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract, *Journal of Ethnopharmacology*, 151(1), pp. 528–535. Available at: https://doi.org/10.1016/j.jep.2013.11.008
29. Kumar N et al (2016) Efficacy of Standardized Extract of Bacopa monnieri (Bacognize®) on Cognitive Functions of Medical Students: A Six-Week, Randomized Placebo-Controlled Trial, *Evidence-based Complementary and Alternative Medicine: eCAM*, 2016, p. 4103423. Available at: https://doi.org/10.1155/2016/4103423
30. Lamport DJ et al (2015) The effect of flavanol-rich cocoa on cerebral perfusion in healthy older adults during conscious resting state: a placebo controlled, crossover, acute trial, *Psychopharmacology*, 232(17), p. 3227. Available at: https://doi.org/10.1007/s00213-015-3972-4
31. Lamport DJ et al (2015) The effect of flavanol-rich cocoa on cerebral perfusion in healthy older adults during conscious resting state: a placebo controlled, crossover, acute trial, *Psychopharmacology*, 232(17), pp. 3227–3234. Available at: https://doi.org/10.1007/s00213-015-3972-4
32. Lamport DJ, Christodoulou E, Achilleos C (2020a) Beneficial Effects of Dark Chocolate for Episodic Memory in Healthy Young Adults: A Parallel-Groups Acute Intervention with a White Chocolate Control., *Nutrients*, 12(2), pp. E483–E483. Available at: https://doi.org/10.3390/nu12020483
33. Lamport DJ, Christodoulou E, Achilleos C (2020b) Beneficial Effects of Dark Chocolate for Episodic Memory in Healthy Young Adults: A Parallel-Groups Acute Intervention with a White Chocolate Control, *Nutrients*, 12(2), p. 483. Available at: https://doi.org/10.3390/nu12020483
34. Lin X et al (2014) Protective effect of madecassoside against cognitive impairment induced by D-galactose in mice., *Pharmacology, biochemistry, and behavior*, 124, pp. 434–442. Available at: https://doi.org/10.1016/j.pbb.2014.07.014
35. Livingston G et al (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission., *Lancet (London, England)*, 396(10248), pp. 413–446. Available at: https://doi.org/10.1016/S0140-6736(20)30367-6
36. Lopes Mesquita H et al (2019) β-Caryophyllene causes remyelination and modifies cytokines expression in C57BL/6 mice with experimental autoimmune encephalomyelitis ARTICLE INFO, *Journal of Applied Pharmaceutical Science*, 9(07), pp. 27–033. Available at: https://doi.org/10.7324/JAPS.2019.90704
37. Mastroiacovo D et al (2014) Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study—a randomized controlled trial1, *The American Journal of Clinical Nutrition*, 101(3), p. 538. Available at: https://doi.org/10.3945/ajcn.114.092189
38. Matthews DG et al (2019) Centella Asiatica Improves Memory and Promotes Antioxidative Signaling in 5XFAD Mice, *Antioxidants*, p. 630. Available at: https://doi.org/10.3390/antiox8120630
39. Memory Melt Chocolate (2026) *Gulfood*. Available at: https://www.gulfood.com/gulfood-2026-products/memory-melt-chocolate (Accessed: March 3, 2026)
40. *Mild Cognitive Impairment (MCI)* (no date) *Alzheimer's Association*. Available at: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment
41. Morgan A, Stevens J (2010) Does Bacopa monnieri Improve Memory Performance in Older Persons? Results of a Randomized, Placebo-Controlled, Double-Blind Trial. https://home.liebertpub.com/*acm*, 16(7), pp. 753–759. Available at: https://doi.org/10.1089/acm.2009.0342
42. Nemetchek MD et al (2016) The Ayurvedic plant Bacopa Monnieri inhibits inflammatory pathways in the brain, *Journal of ethnopharmacology*, 197, p. 92. Available at: https://doi.org/10.1016/j.jep.2016.07.073
43. Orhan IE (2012) Centella asiatica (L.) Urban: From Traditional Medicine to Modern Medicine with Neuroprotective Potential, *Evidence-Based Complementary and Alternative Medicine*, 2012(1), p. 946259. Available at: https://doi.org/10.1155/2012/946259
44. Page MJ et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews., *BMJ (Clinical research ed.)*, 372, p. n71. Available at: https://doi.org/10.1136/bmj.n71
45. Pandareesh MD, Anand T (2013) Neuromodulatory Propensity of Bacopa monniera Against Scopolamine-Induced Cytotoxicity in PC12 Cells Via Down-Regulation of AChE and Up-Regulation of BDNF and Muscarnic-1 Receptor Expression, *Cellular and Molecular Neurobiology*, 33(7), p. 875. Available at: https://doi.org/10.1007/s10571-013-9952-5
46. Pase MP et al (2012) The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials, *Journal of alternative and complementary medicine (New York, N.Y.)*, 18(7), pp. 647–652. Available at: https://doi.org/10.1089/acm.2011.0367
47. Peth-Nui T et al (2012) Effects of 12-Week Bacopa monnieri Consumption on Attention, Cognitive Processing, Working Memory, and Functions of Both Cholinergic and Monoaminergic Systems in Healthy Elderly Volunteers, *Evidence-based Complementary and Alternative Medicine: eCAM*, 2012, p. 606424. Available at: https://doi.org/10.1155/2012/606424
48. Puttarak P et al (2017) Effects of Centella asiatica (L.) Urb. on cognitive function and mood related outcomes: A Systematic Review and Meta-analysis, *Scientific Reports*, 7(1), p. 10646. Available at: https://doi.org/10.1038/s41598-017-09823-9

49. Raghav S, Singh H, Dalal PK et al (2006) Randomized controlled trial of standardized Bacopa monniera extract in age-associated memory impairment., *Indian journal of psychiatry*, 48(4), pp. 238–242. Available at: https://doi.org/10.4103/0019-5545.31555
50. Raghav S, Singh H, Dalal P et al (2006a) Randomized controlled trial of standardized Bacopa monniera extract in age-associated memory impairment, *Indian Journal of Psychiatry*, 48(4), p. 238. Available at: https://doi.org/10.4103/0019-5545.31555
51. Raghav S, Singh H, Dalal P et al (2006b) Randomized controlled trial of standardized Bacopa monniera extract in age-associated memory impairment, *Indian Journal of Psychiatry*, 48(4), p. 238. Available at: https://doi.org/10.4103/0019-5545.31555
52. Ricardi C et al (2025) Multi-Target Protective Effects of β-Caryophyllene (BCP) at the Intersection of Neuroinflammation and Neurodegeneration, *International Journal of Molecular Sciences 2025, Vol. 26, Page 6027*, 26(13), p. 6027. Available at: https://doi.org/10.3390/ijms26136027
53. Sathyanarayanan V et al (2013) Brahmi for the better? New findings challenging cognition and anti-anxiety effects of Brahmi (Bacopa monniera) in healthy adults., *Psychopharmacology*, 227(2), pp. 299–306. Available at: https://doi.org/10.1007/s00213-013-2978-z
54. SJ* B et al (2021) Beta-Caryophyllene, an Anti-Inflammatory Natural Compound, Improves Cognition in an Elderly Group who has Concerns about Memory, *Medical Journal of Clinical Trials & Case Studies*, 5(5), pp. 0–0. Available at: https://doi.org/10.23880/mjccs-16000300
55. Speers AB et al (2021) Centella asiatica Alters Metabolic Pathways Associated With Alzheimer's Disease in the 5xFAD Mouse Model of ß-Amyloid Accumulation, *Frontiers in Pharmacology*, 12, p. 788312. Available at: https://doi.org/10.3389/fphar.2021.788312
56. Stough C et al (2008) Examining the nootropic effects of a special extract of Bacopa monniera on human cognitive functioning: 90 day double-blind placebo-controlled randomized trial, *Phytotherapy research: PTR*, 22(12), pp. 1629–1634. Available at: https://doi.org/10.1002/ptr.2537
57. Stringer, T.P., Guerrieri, D. and Van Praag, H. (2015) Plant-derived flavanol (−)epicatechin mitigates anxiety in association with elevated hippocampal monoamine and BDNF levels,but does not influence pattern separation in mice, *Translational Psychiatry*, 5(1), pp. e493–e493. Available at: https://doi.org/10.1038/tp.2014.135
58. Suominen MH et al (2020) The short-term effect of dark chocolate flavanols on cognition in older adults: A randomized controlled trial (FlaSeCo), *Experimental Gerontology*, 136, p. 110933. Available at: https://doi.org/10.1016/j.exger.2020.110933
59. Teerapattarakan N et al (2025) Preclinical neuropharmacological effects of Centella asiatica-derived asiaticoside and madecassoside in Alzheimer's disease, *South African Journal of Botany*, 180, pp. 171–184. Available at: https://doi.org/https://doi.org/10.1016/j.sajb.2025.03.014
60. Valotto Neto LJ et al (2024) Investigating the Neuroprotective and Cognitive-Enhancing Effects of Bacopa monnieri: A Systematic Review Focused on Inflammation, Oxidative Stress, Mitochondrial Dysfunction, and Apoptosis., *Antioxidants (Basel, Switzerland)*, 13(4). Available at: https://doi.org/10.3390/antiox13040393
61. Walsh S et al (2024) Considering challenges for the new Alzheimer's drugs: Clinical, population, and health system perspectives, *Alzheimer's & dementia: the journal of the Alzheimer's Association*, 20(9), pp. 6639–6646. Available at: https://doi.org/10.1002/alz.14108
62. Wattanathorn J et al (2008) Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica, *Journal of Ethnopharmacology*, 116(2), pp. 325–332. Available at: https://doi.org/10.1016/j.jep.2007.11.038
63. Wong JH, Barron AM, Abdullah JM (2021) Mitoprotective Effects of Centella asiatica (L.) Urb.: Anti-Inflammatory and Neuroprotective Opportunities in Neurodegenerative Disease, *Frontiers in Pharmacology*, Volume 12. Available at: https://doi.org/10.3389/fphar.2021.687935
64. *World Health Organization* (2017) No Title. Available at: https://www.who.int/news/item/07-12-2017-dementia-number-of-people-affected-to-triple-in-next-30-years
65. World Health Organization (2025) *Dementia*. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia

Figures

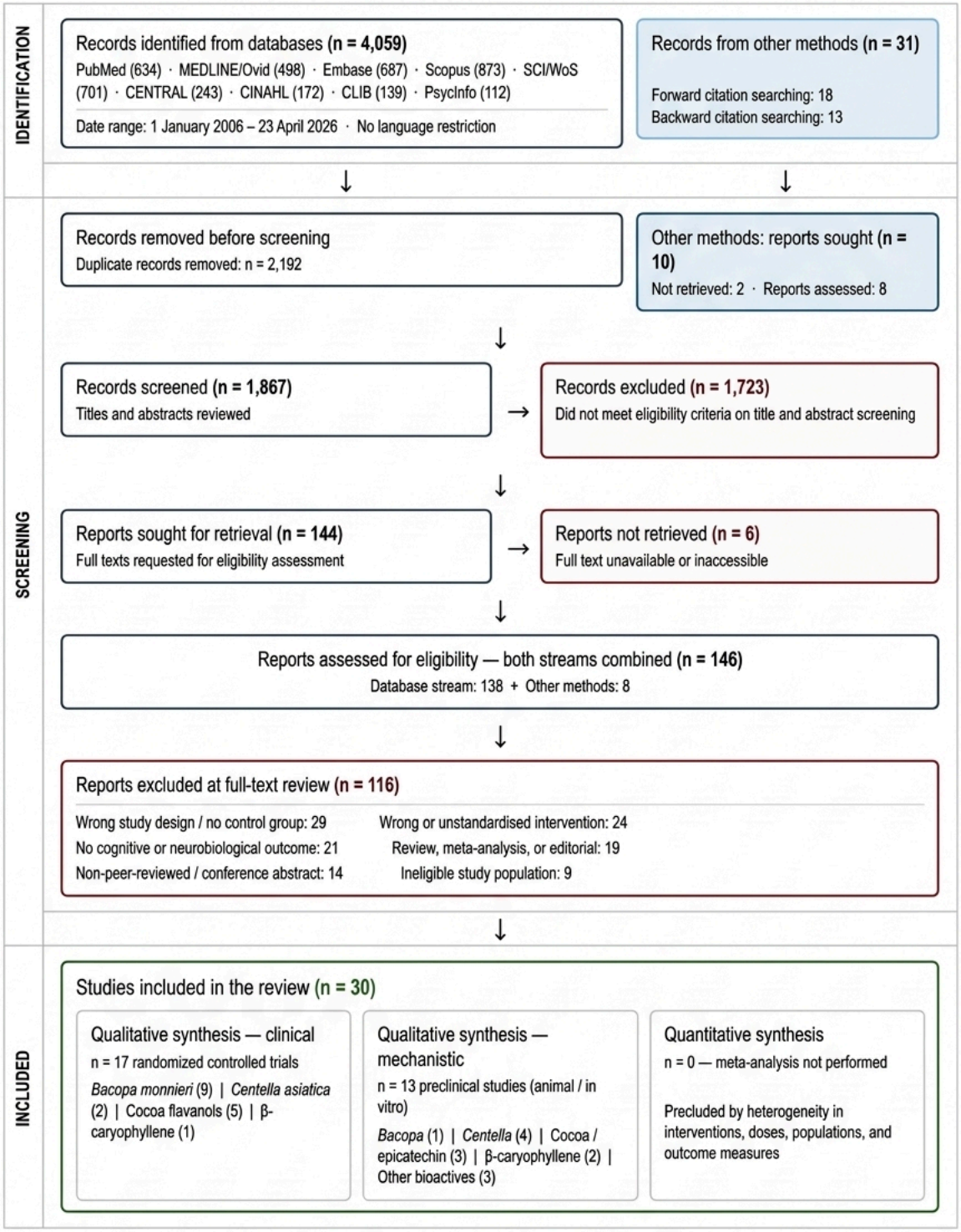

Figure 1

Participant flow diagram for Systematic Review of Randomized Controlled Trials.

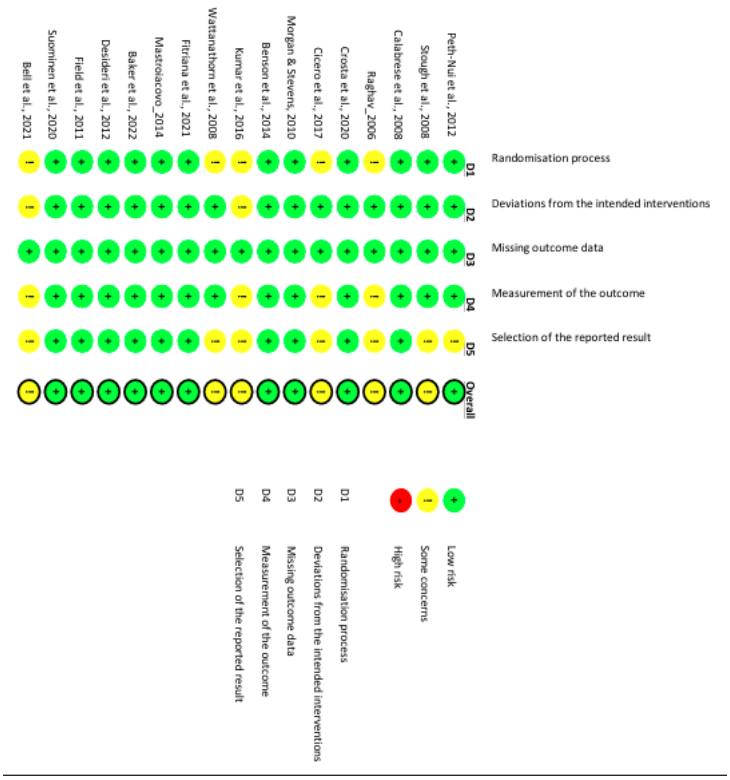

Figure 2

Risk of bias assessment summary of included randomized controlled trial study using the Cochrane RoB 2 tool.

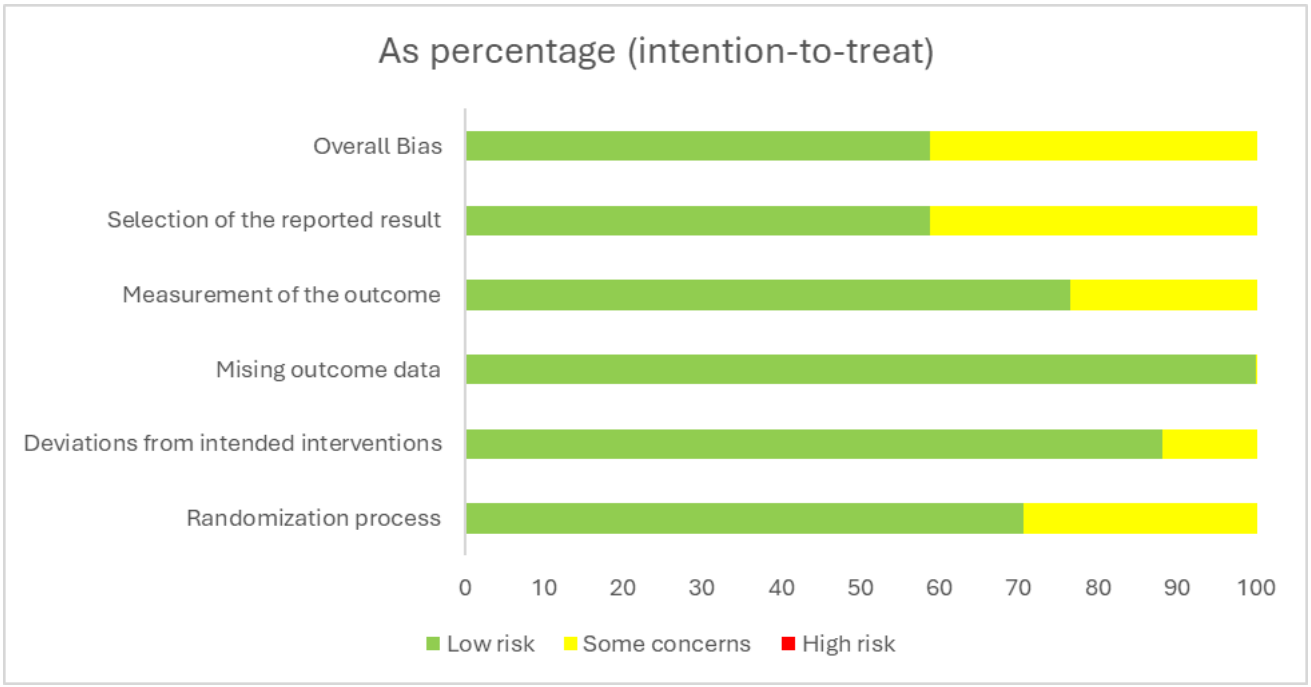

Figure 3

Overall summary of Risk of bias assessment using the Cochrane RoB 2 tool.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S4PICOtable.docx

- S3systematicreviewprotocol.docx
- S2PRISMAchecklist.docx
- S1RoB2assessmentfulldetails.xlsx