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Centella asiatica and Bacopa monnieri in Alzheimer's Disease, Dementia, and Cognitive Impairment: A PRISMA-Compliant Systematic Literature Review with Ethnopharmacological Perspective and Comparative Analysis

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ADMINISTRATIVE INFORMATION

Support - Universiti Kebangsaan Malaysia.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 August 2026 and was last updated on 27 August 2026.

INTRODUCTION

Review question / Objective (1) Document the traditional Ayurvedic and ethnopharmacological foundations for Centella asiatica and Bacopa monnieri for treating cognitive disorders.
(2) Synthesise preclinical animal-study evidence on neuroprotective mechanisms and cognitive outcomes for both plants.
(3) Evaluate human clinical evidence for efficacy and safety in AD, dementia, and cognitive impairment populations.
(4) Characterize and compare the key bioactive compounds and molecular mechanisms of action.
(5) Conduct a head-to-head comparative analysis of both plants.

Rationale Alzheimer's disease (AD) and related cognitive disorders represent a major and increasing global health burden. Current pharmacological treatments, including cholinesterase inhibitors and NMDA receptor antagonists, provide primarily symptomatic benefits and do not halt disease progression. The multifactorial pathophysiology of AD, involving amyloid-β accumulation, tau pathology, oxidative stress, mitochondrial dysfunction, neuroinflammation and synaptic degeneration, supports investigation of multi-target therapeutics.

approaches. Centella asiatica and Bacopa monnieri are traditionally used in Ayurveda as Medhya Rasayanas for memory enhancement and cognitive disorders. Increasing preclinical and clinical evidence suggests that their extracts and bioactive compounds may exert antioxidant, anti-inflammatory, anti-amyloid, cholinergic, mitochondrial, and synaptic effects. However, the evidence is distributed across animal, in vitro, phytochemical, ethnopharmacological and human clinical studies, and the comparative evidence between the two botanicals has not been comprehensively

synthesized. Therefore, this systematic review aims to integrate the available evidence regarding the cognitive, neuroprotective, mechanistic, and

clinical effects of Centella asiatica and Bacopa monnieri in Alzheimer's disease, dementia, and cognitive impairment, while considering their ethnopharmacological background and comparing the evidence for the two interventions.

Condition being studied Alzheimer's disease, dementia, mild cognitive impairment, age-associated cognitive impairment/memory impairment, and related cognitive dysfunction.

METHODS

Search strategy ("Centella asiatica" [Title/Abstract] OR ("Gotu Kola"[Title/Abstract] OR asiaticoside[Title/Abstract]) AND ("Alzheimer's disease"[Title/Abstract] OR dementia[Title/Abstract] OR "cognitive impairment" [Title/Abstract]) AND (neuroprotection[Title/Abstract] OR "amyloid-beta" [Title/Abstract] OR memory[Title/Abstract] OR acetylcholinesterase [Title/Abstract] OR "oxidative stress" [Title/Abstract]).

Participant or population The population includes humans with Alzheimer's disease, dementia, mild cognitive impairment, age-associated memory impairment, or other clinically relevant cognitive impairment, as well as validated experimental animal models of Alzheimer's disease or cognitive impairment. The review also includes relevant in vitro/cellular models when investigating neuroprotective or cognitive-related mechanisms of Centella asiatica, Bacopa monnieri, or their bioactive compounds.

Intervention Centella asiatica (L.) Urban and Bacopa monnieri (L.) Wettst., including whole-plant preparations, extracts, standardized extracts, formulations, and isolated bioactive compounds derived from these plants. Relevant bioactive compounds include asiaticoside, madecassoside, asiatic acid, and caffeoylquinic acids from Centella asiatica; and bacosides, bacoside A, bacopaside I, plantainoside B, and ebelin lactone from Bacopa monnieri.

Comparator Comparators were not uniform because the review included heterogeneous preclinical, clinical, in vitro, phytochemical, ethnopharmacological, and review studies. Where applicable, eligible studies included placebo/vehicle controls, untreated or baseline controls, conventional pharmacological comparators such as donepezil, alternative interventions such as folic acid, or other appropriate experimental controls. Studies without an appropriate control group for evaluating cognitive outcomes were excluded.

Study designs to be included Eligible evidence includes human clinical trials, animal experimental studies, in vitro/cellular studies, phytochemistry studies, ethnopharmacological studies, systematic reviews/meta-analyses and other mixed-methods studies relevant to the review question.

Eligibility criteria Studies were eligible if they met the following criteria:

1. Investigated Centella asiatica, Bacopa monnieri, or isolated bioactive compounds from these plants as the primary intervention/exposure.
2. Addressed Alzheimer's disease, dementia, or cognitive impairment in human populations or validated animal models.
3. Reported cognitive, neuroprotective, amyloid-β, oxidative-stress, or molecular/mechanistic outcomes.
4. Addressed the traditional Ayurvedic or ethnopharmacological use of these plants in relation to memory or cognitive disorders.
5. Provided sufficient information regarding the botanical intervention, extract/compound characteristics, and relevant experimental or clinical outcomes.

Information sources Electronic bibliographic and scholarly information sources: PubMed, Google Scholar, SciSpace Basic Search, and SciSpace Full Text Search. The search covered publications from 2006 through August 2026.

Main outcome(s) Cognitive function and memory performance are assessed using validated cognitive tests or behavioral measures in human and animal studies, including measures of learning, memory, executive function, information processing, and related cognitive performance.

Additional outcome(s) Secondary/additional outcomes include:

1. Neuroprotective effects.
2. Amyloid-β levels, deposition, and aggregation.
3. Tau phosphorylation/pathology.
4. Acetylcholinesterase activity and cholinergic function.
5. Oxidative stress and antioxidant responses, including NRF2-related pathways.
6. Neuroinflammatory markers and NF-κB/cytokine-related pathways.
7. Mitochondrial function and bioenergetics.
8. Synaptic density, synaptic plasticity, and long-term potentiation.
9. BDNF/TrkB/ERK-related signaling.
10. Molecular mechanisms of action.

11. Bioactive compounds and phytochemical composition.
12. Pharmacokinetic/bioavailability findings were reported.
13. Safety, tolerability, and adverse events in human studies.
14. Comparative efficacy between Centella asiatica and Bacopa monnieri and against conventional comparators.

Data management Data were extracted from eligible studies using a standardized data extraction framework. The extracted variables were study type, plant intervention/focus, bioactive compounds, mechanisms of action, cognitive outcomes and tests, and key findings. The extracted information was organized to allow for comparison and qualitative synthesis across categories of studies.

Quality assessment / Risk of bias analysis Risk-of-bias assessment was performed across all 242 included studies. Table 1 summarizes the distribution of RoB judgments by study design. The large proportion of studies rated as UNCLEAR (241/242; 99.6%) reflects a pervasive under-reporting of methodological detail in the available literature: randomization procedures, blinding, allocation concealment, and outcome-selection transparency were rarely described with sufficient clarity to permit a definitive LOW or MODERATE judgement from abstracts and available metadata alone. Only one study (<0.5%) provided sufficient methodological reporting to warrant a MODERATE risk-of-bias rating; no study achieved a LOW rating. This finding is itself a significant outcome of the review, indicating a systematic transparency gap across the corpus.

Strategy of data synthesis Due to substantial heterogeneity in study designs, populations, experimental models, botanical preparations, doses, outcomes, and outcome measurement methods, findings will be synthesized primarily through structured qualitative/narrative synthesis. Studies will be grouped according to study design, botanical intervention (Centella asiatica, Bacopa monnieri, or both), population/model, and outcome domain. Evidence will be compared with respect to cognitive effects, neuroprotective mechanisms, bioactive compounds, clinical efficacy, safety, and comparative effects. Mechanistic findings will be integrated across preclinical and clinical evidence to identify convergent pathways and differences between the two botanicals.

Subgroup analysis The manuscript does not formally specify prespecified subgroup analyses.

Sensitivity analysis No formal sensitivity analysis was reported. Because of the heterogeneous evidence base, sensitivity analyses were not applicable to the overall qualitative synthesis.

Language restriction No language restrictions were applied.

Country(ies) involved Malaysia.

Other relevant information This systematic literature review was conducted according to the PRISMA 2020 framework. The review incorporated heterogeneous evidence, including animal studies, human clinical trials, in vitro investigations, phytochemical studies, ethnopharmacological studies, reviews/meta-analyses, and mixed-methods studies. A structured data-extraction framework was applied across the included studies, covering study type, botanical intervention, bioactive compounds, mechanisms of action, cognitive outcomes and key findings. The review ultimately included 242 studies following screening and eligibility assessment. AI-assisted tools were used to facilitate literature retrieval, screening, structured data extraction, and manuscript organization; all AI-assisted outputs were subsequently reviewed and edited by the authors, citations were verified, extracted information was cross-checked against primary sources, and the authors retained responsibility for the accuracy and integrity of the manuscript. The registration is being submitted retrospectively, after completion of the literature search, screening, data extraction, and synthesis.

Keywords Centella asiatica; Bacopa monnieri; Alzheimer's disease; dementia; mild cognitive impairment; cognitive impairment; cognitive enhancement; neuroprotection; ethnopharmacology; Ayurvedic medicine; Medhya Rasayana.

Dissemination plans The findings of this systematic review will be disseminated through publication in a peer-reviewed international scientific journal and through academic and scientific communication. The manuscript is intended to contribute to the evidence base concerning the neuroprotective and cognitive effects of Centella asiatica and Bacopa monnieri and to inform future preclinical and clinical research.

Contributions of each author
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