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Depression and Depression-Related Mechanistic Evidence for Centella asiatica and Its Triterpenoids: A Scoping Review of Cell-Based, Animal, and Human Studies

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

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 2 July 2026 and was last updated on 5 July 2026.

INTRODUCTION

Review question / Objective This scoping review asks: What cell-based, animal, and human evidence is available on the effects of Centella asiatica, standardized extracts, and its bioactive triterpenoids in relation to depression, depressive-like behavior, antidepressant-like effects, and biological mechanisms explicitly linked to depression-related pathophysiology?
The primary objective is to map the available cell-based, animal, and human evidence on Centella asiatica, standardized extracts, and bioactive triterpenoids in relation to depression, depressive symptoms, depressive-like behavior, antidepressant-like effects, and depression-related mechanistic pathways.
The secondary objective is to identify translational gaps related to clinical evidence, dosing, extract standardization, outcome measures, safety, and mechanistic validation for future depression-focused research.

Background Depression is a major public health problem and remains associated with substantial morbidity, functional impairment, and treatment limitations. Although conventional antidepressants are effective for many patients, incomplete response, delayed onset of action, adverse effects, and relapse risk continue to support interest in adjunctive or alternative therapeutic candidates with multitarget biological effects.
Centella asiatica (L.) Urb., commonly known as Gotu kola, is a medicinal plant traditionally used for neurological, cognitive, wound-healing, and anti-inflammatory purposes. Its major bioactive constituents include triterpenoids such as asiatic acid, asiaticoside, madecassic acid, madecassoside, madasiatic acid, and standardized triterpenoid-rich extracts. These compounds have been investigated in experimental systems relevant to neuropsychiatric disorders, including oxidative stress, neuroinflammation, mitochondrial dysfunction, HPA-axis dysregulation, monoamine neurotransmission, BDNF/CREB signaling, and neuroplasticity.

Preclinical studies suggest that C. asiatica and its triterpenoids may influence depressive-like behavior, stress-related responses, anxiety-related outcomes, and depression-relevant biological pathways. Limited human evidence has also reported mood-, anxiety-, or stress-related outcomes, although direct clinical evidence for major depressive disorder remains insufficient. Existing reviews have discussed C. asiatica in broader neuroprotective, cognitive, or mood-disorder contexts; however, the evidence has not been comprehensively mapped across cell-based, animal, and human studies with a specific focus on depression-relevant mechanistic and translational evidence.

Therefore, this scoping review aims to systematically map the available evidence on C. asiatica, standardized extracts, and its bioactive triterpenoids in relation to depression-relevant mechanisms and outcomes. The review will identify the types of evidence available, summarize studied models and outcomes, clarify mechanistic pathways, and highlight translational gaps related to clinical evidence, dosing, extract standardization, safety, and future research priorities.

Rationale The evidence on Centella asiatica and its triterpenoids is broad and includes neuroprotective, cognitive, anxiolytic, stress-related, and mood-related studies. However, the present review aims to focus specifically on depression and depression-related conditions. This amendment clarifies that studies will be included only when they report direct depression-related outcomes, depressive-like behavior, antidepressant-like effects, or mechanistic endpoints explicitly linked to depression-related pathophysiology.

This narrower focus will prevent overextension into general neuroprotection, cognition, anxiety-only, or stress-only literature, while still allowing inclusion of mechanistic studies when the mechanisms are clearly interpreted in relation to depression or depressive-like phenotypes.

METHODS

Strategy of data synthesis The original search strategy will be retained because it was designed to be sensitive and to capture potentially relevant depression-related mechanistic evidence. No new database search is planned. The same databases and registry sources will be used: Scopus, PubMed/MEDLINE, Cochrane Library/CENTRAL, and ClinicalTrials.gov, searched from inception to 2 July 2026.

During screening and synthesis, however, eligibility will be narrowed to studies reporting depression, depressive symptoms, depressive-like behavior, antidepressant-like effects, major depressive disorder, depression-related experimental models, or biological mechanisms explicitly linked to depression-related pathophysiology.

Findings will be synthesized descriptively and narratively. Evidence will be grouped by study type, including cell-based or ex vivo studies, animal studies, and human studies. Studies will also be categorized by intervention type, including crude extracts, standardized extracts, total triterpenes, and isolated compounds. Mechanistic findings will be mapped according to depression-related pathways, including HPA-axis activity, monoamine neurotransmission, BDNF/CREB signaling, neuroinflammation, oxidative stress and Nrf2 signaling, mitochondrial function, and neuroplasticity. No meta-analysis is planned because substantial heterogeneity is expected across models, interventions, outcomes, and mechanisms.

Eligibility criteria This scoping review will include original cell-based, ex vivo, animal, and human studies that evaluate Centella asiatica, Gotu kola, standardized C. asiatica extracts, total triterpenes, or clearly identified C. asiatica-derived compounds in relation to depression, depressive-like behavior, antidepressant-like effects, or mechanisms explicitly linked to depression-related pathophysiology.

Eligible populations will include humans, animals, cell-based models, or ex vivo models relevant to depression, depressive symptoms, depressive-like behavior, antidepressant-like effects, or depression-related biological mechanisms. Human studies may include healthy participants or clinical populations if depression-related outcomes are reported, including depressive symptoms, depression rating scales, major depressive disorder, or depression-related mood outcomes.

Eligible depression-related animal models and outcomes may include chronic unpredictable mild stress, chronic mild stress, chronic restraint stress when used as a depression model, olfactory bulbectomy, forced swim test, tail suspension test, sucrose preference test, or other validated depressive-like behavioral outcomes.

Eligible mechanistic endpoints include HPA-axis activity, cortisol or corticosterone, monoamine neurotransmission, serotonin, dopamine, norepinephrine or noradrenaline, BDNF/CREB signaling, neuroinflammation, NF-κB/NLRP3 signaling, oxidative stress, Nrf2 signaling, mitochondrial function, neuroplasticity, neurogenesis, or synaptic outcomes when these

are explicitly linked to depression or depressive-like behavior.
Studies focused only on anxiety, stress, cognition, Alzheimer's disease, Parkinson's disease, stroke, epilepsy, brain injury, general neuroprotection, or other non-depression conditions will be excluded unless they report a depression-related outcome or provide mechanistic evidence explicitly interpreted in relation to depression or depressive-like behavior.
Polyherbal formulations will be excluded unless they include a Centella asiatica-only comparison arm, are standardized to C. asiatica triterpenoids, or provide extract-specific findings attributable to C. asiatica. Reviews, editorials, commentaries, letters, book chapters, protocols, conference abstracts without sufficient original data, pure phytochemical or extraction studies without depression-related outcomes, and purely computational studies will be excluded. Molecular docking, molecular dynamics simulation, network pharmacology, and in silico ADMET studies will be excluded unless they are part of an article that also reports eligible cell-based, animal, or human experimental data.

Source of evidence screening and selection All retrieved records will be imported into reference-management software, and duplicates will be removed before screening. The same retrieved record set will be re-screened using the amended depression-focused eligibility criteria.
The selection process will be conducted in two stages. First, two reviewers will independently screen titles and abstracts against the amended eligibility criteria. Records will be retained for full-text assessment when they report or clearly suggest depression, depressive symptoms, depressive-like behavior, antidepressant-like effects, major depressive disorder, depression-related animal models, or mechanisms explicitly linked to depression-related pathophysiology.
Records will be excluded at title/abstract screening if they are clearly unrelated to depression or depression-related mechanisms, including anxiety-only, stress-only, cognition-only, general neuroprotection, Alzheimer's disease, Parkinson's disease, stroke, epilepsy, or other neurological studies without depression-related outcomes or depression-linked mechanistic interpretation.
Second, the full texts of potentially eligible studies will be retrieved and independently assessed by two reviewers. Reasons for exclusion at the full-text stage will be recorded, including wrong intervention or compound, no depression-related outcome, no depression-linked mechanism, ineligible study design, review or other non-original publication, pure phytochemical or extraction study without relevant outcomes, purely computational study without eligible experimental data, or unavailable English full text. Disagreements will be resolved through discussion, with consultation of a third reviewer when necessary.

Data management Search results from each database will be exported and imported into reference-management software for organization and duplicate removal. After deduplication, records will be transferred to a screening platform or structured spreadsheet for title/abstract and full-text screening.

A standardized data-charting form will be developed before extraction and piloted on a small sample of included studies. Extracted data will include bibliographic details, study design, model or population, intervention or compound, comparator, dose, route, duration, outcome measures, mechanistic endpoints, safety findings, and key conclusions.

Screening decisions, reasons for full-text exclusion, and extracted data will be recorded systematically. Any changes to the extraction form during the review process will be documented. Final datasets will be stored securely in password-protected institutional or cloud storage accessible only to the review team.

Reporting results / Analysis of the evidence The evidence will be analyzed descriptively and narratively. Included studies will be grouped according to study type, intervention type, and depression-related outcome domain. The main synthesis will prioritize direct depression evidence, including depressive symptoms, depressive-like behavior, antidepressant-like effects, major depressive disorder, depression rating scales, and depression-related experimental models.
Mechanistic evidence will be summarized when the biological pathway is explicitly linked to depression or depressive-like behavior. These pathways may include HPA-axis regulation, monoamine neurotransmission, BDNF/CREB signaling, neuroinflammation, oxidative stress and Nrf2 signaling, mitochondrial function, neuroplasticity, neurogenesis, and synaptic function.
Studies without direct depression outcomes will not be included unless their mechanistic findings are explicitly interpreted in relation to depression-related pathophysiology.

Presentation of the results Results will be presented using a PRISMA-style flow diagram and

structured tables. Tables will summarize study characteristics, model or population, Centella asiatica preparation or compound, comparator, dose, route, duration, depression-related outcomes, mechanistic endpoints, safety findings, and key conclusions.
The narrative synthesis will be organized around: (1) direct depression-related evidence; (2) depression-related animal models; (3) cell-based or ex vivo mechanistic evidence linked to depression; (4) human evidence; and (5) translational gaps related to clinical evidence, dosing, extract standardization, outcome measurement, safety, and mechanistic validation.

Language restriction English.

Country(ies) involved Thailand.

Other relevant information This amendment was made before final screening, data extraction, and evidence synthesis. The purpose of the amendment is to clarify and narrow the scope of the review so that the final review focuses on depression, depressive-like behavior, antidepressant-like effects, and mechanisms explicitly linked to depression-related pathophysiology. The original search strategy was intentionally broad to maximize sensitivity; therefore, no new database search is planned. The retrieved records will be re-screened using the amended depression-focused eligibility criteria.

Keywords Centella asiatica; Gotu kola; depression; depressive-like behavior; antidepressant-like effect; triterpenoids; asiatic acid; asiaticoside; madecassic acid; neuroinflammation; oxidative stress; scoping review.

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