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Depression-Relevant Mechanistic and Translational 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 2 July 2026.

INTRODUCTION

Review question / Objective This scoping review asks: What cell-based, animal, and human evidence is available on the depression-relevant mechanistic and translational effects of Centella asiatica, standardized extracts, and its bioactive triterpenoids?
Using the PCC framework, the Population includes humans, animals, cell-based models, and ex vivo models relevant to depression, depressive-like behavior, stress, anxiety, mood-related outcomes, or depression-relevant biological mechanisms. The Concept is Centella asiatica, Gotu kola, standardized C. asiatica extracts, total triterpenes, asiatic acid, asiaticoside, madecassic acid, madecassoside, madasiatic acid, and other clearly identified C. asiatica-derived compounds. The Context is depression-relevant mechanistic and translational evidence, including depressive-like behavior, stress-related or anxiety-related outcomes, mood-related outcomes, anxiety/depression scales, HPA-axis activity, monoamine neurotransmission, BDNF/CREB signaling, neuroinflammation, oxidative stress, mitochondrial function, and neuroplasticity.
The primary objective is to map the available cell-based, animal, and human evidence on depression-relevant mechanistic and translational effects of C. asiatica, standardized extracts, and its bioactive triterpenoids. The secondary objective is to identify translational gaps related to clinical evidence, dosing, extract standardization, outcome measures, safety, and mechanistic validation.

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 in depression-related research is heterogeneous and distributed across cell-based studies, animal models, and limited human studies. These studies assess different preparations, including crude extracts, standardized extracts, total triterpenes, and isolated compounds such as asiatic acid, asiaticoside, madecassic acid, madecassoside, and madasiatic acid. Outcomes also vary widely, including depressive-like behavior, anxiety- or stress-related outcomes, mood-related clinical scales, neuroinflammatory markers, oxidative stress, HPA-axis activity, monoamine neurotransmission, BDNF/CREB signaling, mitochondrial function, and neuroplasticity.

Because of this heterogeneity, a scoping review is more appropriate than a conventional systematic review or meta-analysis. A scoping approach will allow mapping of the available evidence, clarification of which models and outcomes have been studied, identification of the main depression-relevant biological pathways, and recognition of gaps that limit clinical translation.

Existing reviews have discussed C. asiatica in broader neuroprotective, cognitive, mood-disorder, or natural-product contexts. However, a structured review specifically focused on depression-relevant mechanistic and translational evidence across cell-based, animal, and human studies remains needed. This review will therefore help define the current evidence landscape and guide future experimental and clinical research on C. asiatica and its triterpenoids as potential depression-related therapeutic candidates.

METHODS

Strategy of data synthesis Scopus, PubMed/MEDLINE, Cochrane Library/CENTRAL, and ClinicalTrials.gov will be searched from database inception to July 2, 2026. In the Cochrane Library, the search will focus on CENTRAL/Trials records. Reference lists of included studies and relevant reviews will also be manually screened.

Search terms will combine keywords related to Centella asiatica and its bioactive constituents with depression-, stress-, anxiety-, mood-, and mechanism-related terms. Search terms will include: “Centella asiatica,” “Gotu kola,” “Hydrocotyle asiatica,” “Indian pennywort,” “standardized extract,” “total triterpenes,” “asiatic acid,” “asiaticoside,” “madecassic acid,” “madecassoside,” “madasiatic acid,” “depression,” “depressive-like behavior,” “antidepressant,” “major depressive disorder,” “mood,” “anxiety,” “stress,” “HPA axis,” “cortisol,” “corticosterone,” “monoamine,” “serotonin,” “dopamine,” “norepinephrine,” “BDNF,” “CREB,” “neuroinflammation,” “NF-κB,” “NLRP3,” “oxidative stress,” “Nrf2,” “mitochondrial function,” and “neuroplasticity.” Search strategies will be adapted for each database.

Retrieved records will be exported to reference-management software, and duplicates will be removed. Titles and abstracts will be screened against the eligibility criteria, followed by full-text assessment of potentially eligible studies. Data will be charted using a standardized extraction form.

Findings will be synthesized descriptively and narratively. Evidence will be grouped by study type: cell-based/ex vivo studies, animal studies, and human studies. Additional grouping will be performed by intervention type, including crude extracts, standardized extracts, total triterpenes,

and isolated compounds. Mechanistic findings will be mapped according to depression-relevant pathways, including HPA-axis activity, monoamine neurotransmission, BDNF/CREB signaling, neuroinflammation, oxidative stress, 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-relevant mechanisms or outcomes.

Population: Eligible populations will include humans, animals, cell-based models, or ex vivo models relevant to depression, depressive-like behavior, stress, anxiety, mood-related outcomes, or depression-relevant biological mechanisms. Human studies may include healthy participants or clinical populations if depression-, anxiety-, stress-, or mood-related outcomes are reported.

Concept: Eligible interventions or exposures will include Centella asiatica, Gotu kola, standardized C. asiatica extracts, total triterpenes, asiatic acid, asiaticoside, madecassic acid, madecassoside, madasiatic acid, and other clearly identified C. asiatica-derived compounds. Polyherbal formulations will be excluded unless they include a C. asiatica-only comparison arm, are standardized to C. asiatica triterpenoids, or provide extract-specific findings relevant to C. asiatica.

Context: Eligible studies must report depression-relevant mechanistic or translational evidence, including depressive-like behavior, stress-related outcomes, anxiety-related outcomes, mood-related outcomes, anxiety or depression scales, HPA-axis activity, cortisol or corticosterone, monoamine neurotransmission, serotonin, dopamine, norepinephrine, BDNF/CREB signaling, neuroinflammation, NF-κB/NLRP3 signaling, oxidative stress, Nrf2 signaling, mitochondrial function, or neuroplasticity.

Eligible study designs will include human randomized controlled trials, nonrandomized clinical studies, observational human studies, animal experimental studies, and cell-based or ex vivo mechanistic studies. Reviews, editorials, commentaries, letters, book chapters, protocols, conference abstracts without sufficient original data, pure phytochemical or extraction studies without neuropsychiatric 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. English-language full-text articles will be included.

Source of evidence screening and selection All retrieved records will be imported into reference-management software, and duplicates will be removed before screening. The selection process will be conducted in two stages. First, two reviewers will independently screen titles and abstracts against the predefined eligibility criteria. Records judged as clearly irrelevant by both reviewers will be excluded. 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, such as wrong intervention or compound, no depression-, anxiety-, stress-, mood-, or neuropsychiatric mechanism-related outcome, ineligible study design, review article, pure phytochemical or extraction study without relevant outcomes, purely computational study without eligible experimental data, or unavailable English full text.

Disagreements between reviewers at any stage will be resolved through discussion. If consensus cannot be reached, a third reviewer or senior reviewer will be consulted. The study selection process will be documented using a PRISMA-style flow diagram, including numbers of records identified, duplicates removed, records screened, full-text articles assessed, and studies included in the final scoping review.

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.

Language restriction English.

Country(ies) involved Thailand.

Keywords Centella asiatica; Gotu kola; depression; triterpenoids; asiatic acid; asiaticoside; neuroinflammation; oxidative stress; scoping review.

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