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Review Article

Centella asiatica: Bridging Traditional Therapeutics and Modern Evidence Pharmacological Potential, Clinical Outcomes, and Research Gaps

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Abstract

Centella asiatica (L.) Urb., commonly known as gotu kola or Mandukaparni, is a medicinal plant widely investigated in modern phytotherapy. Its therapeutic effects are mainly attributed to pentacyclic triterpenoids, particularly asiaticoside, madecassoside, asiatic acid, and madecassic acid. These compounds may modulate inflammatory pathways, enhance antioxidant defenses through nuclear factor E (Nrf2) signaling, and influence extracellular matrix remodeling. This review summarizes the current evidence regarding the therapeutic applications, mechanisms, efficacy, safety, and research gaps associated with *C. asiatica*. Available evidence indicates potential benefits in wound healing, scar management, chronic venous insufficiency, and related microangiopathies. However, evidence for cognitive enhancement and anti-aging effects remains inconsistent, with clinical studies limited by small sample sizes, heterogeneous formulations, variable doses, and inadequate standardization of triterpenoid content. The oral bioavailability of its glycosides may also be limited by gastrointestinal metabolism. Although *C. asiatica* has a generally favorable short-term safety profile, rare cases of hepatotoxicity have been reported, particularly with high-dose use. Overall, *C. asiatica* shows promising therapeutic potential, especially for wound healing and venous disorders, but stronger clinical evidence is required for neurological and anti-aging applications. Future research should emphasize standardized extracts, dose-ranging studies, pharmacokinetic-pharmacodynamic relationships, and well-designed clinical trials.

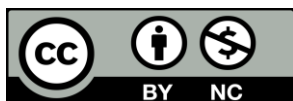
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1.Introduction:

Centella asiatica occupies a unique position in the field of botanical medicine. It has parallel and independent histories in Ayurveda, where it is referred to as a medhya Rasayana *Centella asiatica* rejuvenator of intellect; in traditional Chinese medicine, where records of its use date back to at least the Eastern Han dynasty; and in Southeast Asian and Malagasy folk practices, where its leaves are used both medicinally and as vegetables. This distinguishes it from many herbs that are primarily used within a single healing tradition in India. Its extensive traditional use has contributed to its recognition as one of the most extensively researched single-plant pharmacopeias in the literature over the past 40 years. A bibliometric analysis of the Scopus database revealed over a thousand indexed publications on the species and its constituents, with a significant increase in research output over the last decade.

The active constituent profile of *C. asiatica* is relatively simple, which has facilitated its investigation compared to that of many polyherbal treatments. Four closely related pentacyclic triterpenoids, asiaticoside and madecassoside, which are triterpene glycosides, and asiatic acid and madecassic acid, their corresponding aglycones formed primarily through gut and hepatic biotransformation following oral administration, account for much of the pharmacological activity attributed to *Centella asiatica*. These compounds are widely used as chemical markers for the standardization of *C. asiatica* extracts, along with secondary flavonoids, caffeoylquinic acids, and volatile terpenes. They also provide a basis for the mechanistic framework underlying many therapeutic applications discussed below [1]. The clinical evidence is the strongest when a somewhat direct mechanism is suggested. Topical application of triterpenoids stimulates fibroblast collagen synthesis, modulates TGF- β /Smad signaling, and promotes angiogenesis. These effects have been confirmed in a sizable number of randomized trials and clearly translate into better wound closure and less scarring. As one moves toward more diffuse, centrally mediated outcomes, such as mood, anxiety, and cognition, the case becomes increasingly unclear. Preclinical rodent data are plentiful and frequently striking, but human trials are small, inconsistent in dosage and extract standardization, and, in the case of cognitive endpoints in particular, have failed to demonstrate a significant effect versus placebo on meta-analytic pooling [2]. A major problem in this review is the discrepancy between preclinical results, clinical confirmation, and mechanistic plausibility of the results. Currently available reviews of *Centella asiatica* typically fall into two categories: broad pharmacological surveys that list the plant's reported activities across almost every organ system without much critical weighting of evidence quality, and more focused, domain-specific reviews that delve deeply into a single

application, such as skin health, neuroprotection, or diabetes, but do not integrate across domains to identify the common bottlenecks (poor bioavailability, lack of standardization, small trial sizes) that recur regardless of the indication being studied. The review proceeds through the main applications, evaluates the consistency and strength of the evidence at each stage, clearly identifies the areas in which preclinical and clinical evidence differ, and concludes with a gap analysis intended more for researchers planning the next generation of trials than for practitioners seeking a therapeutic conclusion. This review is purposefully limited in its breadth. We focused on evidence published since approximately 2016, using foundational older studies *Centella asiatica* especially microcirculatory trials from the 1990s and the 2000s that continue to form the basis of the literature on venous insufficiency *Centella asiatica* only when they support a claim that has not been superseded by more recent research. Since the conflation of these levels of evidence is one of the more persistent issues in the secondary literature on this plant, we limited ourselves to peer-reviewed primary studies, systematic reviews, and meta-analyses. We also distinguished between findings established in cell cultures, rodent models, and humans [3,4].

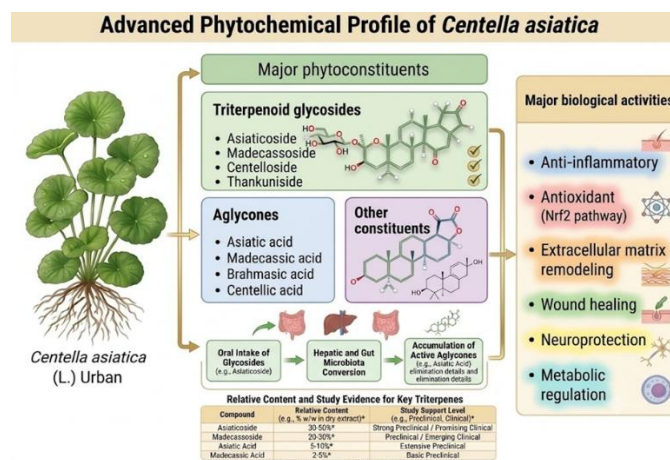


Figure 1. Detailed Phytochemical profile and Biological Activities of *Centella asiatica*

2. Pharmacokinetics, Phytochemistry and Standardization

2.1 The issue of standards and chemical components

Centella asiatica produces more than 50 secondary metabolites. Among them are flavonoids, volatile mono- and sesquiterpenes pentacyclic triterpenoids and their glycosides, and a group of alkaloid compounds, including vellarine and hydrocotyline [5]. Important bioactive markers in the plant are the triterpenoid saponins asiaticoside and madecassoside. Their aglycones, acids, and madecassic acid are also frequently linked to pharmacological effects in preclinical studies [6]. A study

comparing 14 accessions of *Centella asiatica* found that the total triterpenoid content varied significantly across samples. Both the genetic background of the plant and the growing conditions played a role in this variation. The reported levels of these compounds vary depending on the accession, the region where the plant was grown, and the season of harvest. Unstandardized *Centella asiatica* extract is neither chemically nor pharmacologically defined. For example, the asiaticoside content of raw materials has been reported to range from approximately 0.5% to 3.7%, whereas madecassoside levels have been reported to range from 0.3% to more than 6%. This lack of consistency creates challenges in the interpretation of research findings. When studies use a standardized extract, such as ECa 233, a preparation developed in Thailand with a fixed ratio of madecassoside (approximately 53%) and asiaticoside (approximately 32%), comparisons of dosing and pharmacokinetic parameters become more meaningful. However, much of the clinical literature refers to “*Centella asiatica* extract” without specifying its triterpenoid content, making comparisons between studies difficult to achieve. This limitation also leaves it unclear whether a study found no effect because the treatment was ineffective or because the dose of the active constituents was insufficient. This issue was highlighted in a 2020 network meta-analysis by Kongkaew et al., which included five trials on wrinkle reduction. The authors noted that the lack of homogeneity across trials was a barrier to drawing clear conclusions regarding treatment effectiveness. Owing to these standardization issues, researchers have increasingly focused on extraction technologies. Compared to conventional methods, such as maceration, newer techniques, including ultrasound-assisted, microwave-assisted, and supercritical CO₂ extraction, can improve the recovery of the four major triterpenoids while also producing extracts with enhanced antioxidant capacity. These environmentally friendly approaches are increasingly being combined with quality control techniques, such as HPLC and UPLC, to ensure consistent phytochemical composition and dosing in future clinical studies [7].

2.2 Pharmacokinetics and bioavailability

A key point that is often overlooked in reviews is that the parent glycosides, asiaticoside and madecassoside, are poorly absorbed as intact compounds in the gastrointestinal (GI) tract. Although these compounds are absorbed, with peak plasma concentrations reported within 5–15 min, and are widely distributed to tissues, including the brain, stomach, and skin, rat studies of ECa 233 showed that the oral bioavailability of intact madecassoside and asiaticoside was less than 1%. In a phase 1 study involving a reformulated ECa 233 capsule administered to Thai volunteers, the parent glycosides

were almost undetectable in the blood [8]. In contrast, their metabolites, asiatic acid and madecassic acid, accumulated in a dose-dependent manner, with accumulation being particularly evident after seven days of repeated dosing. This finding is important for the interpretation of pharmacological studies. Much of the activity attributed to asiaticoside or madecassoside in cell cultures or short-term animal studies may not directly reflect their effects in humans. In humans, the corresponding acid metabolites, formed through hepatic and gut microbial metabolism, may represent the predominant circulating forms and potentially contribute substantially to the pharmacological effects of the parent drug. Extrapolating pharmacokinetic findings from one species to another is challenging because the pharmacokinetics of humans do not necessarily follow the patterns observed in rodents. A phase 1 trial in Thai volunteers found that the maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) of ECa 233 metabolites did not scale as expected from previous rat studies. The researchers attributed these differences to interspecies variations in gut microbiota activity and first-pass hepatic metabolism. Another study examined the pharmacokinetics of triterpenes and caffeoylquinic acids over 10 h following the administration of either 2 g or 4 g of an aqueous *Centella asiatica* product to adults with cognitive impairment who were already receiving cholinesterase inhibitors. This study confirmed that dosing was associated with increased expression of NRF2-pathway genes in peripheral blood cells. This finding provides a direct human biomarker link between oral *C. asiatica* intake and activation of an antioxidant-related pathway that has been more commonly investigated in animal models, including mouse brain tissue [9].

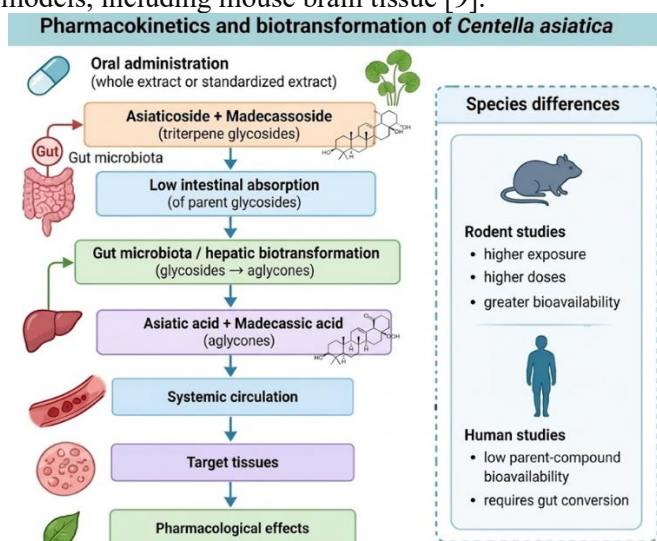


Figure 2. Pharmacokinetic pathway and biotransformation of *Centella asiatica* with species differences

3. Dermatological Uses: Skin Aging, Scar Modulation and Wound Healing

3.1 Mechanistic foundation

The most detailed evidence for *C. asiatica* comes from dermatological research. Asiaticoside and its metabolite, asiatic acid, appear to influence multiple stages of the wound-healing process. During the inflammatory phase, these compounds may help regulate the initial inflammatory response without completely suppressing it, partly through modulation of NF- κ B signaling and reduction of pro-inflammatory mediators such as TNF- α , IL-6, and inducible nitric oxide synthase. During the proliferative phase, asiaticoside has been reported to increase the production of fibronectin and types I, II, and III collagen. It may also enhance the expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which can promote early angiogenesis through pathways involving TGF- β receptor-dependent signaling. An important finding emerged from studies on mice with experimentally induced scars. Asiaticoside treatment reduced the deposition of collagen types I and III, decreased scar thickness, and reduced the expression of TGF- β 1. These findings suggest that asiaticoside may limit fibrosis during the wound healing remodeling phase. This effect is associated with the activation of Smad7, which inhibits TGF- β receptor I signaling and reduces myofibroblast formation. Therefore, the current evidence suggests that *Centella asiatica* may exert dual effects during wound healing by supporting collagen synthesis during tissue repair and limiting excessive scar formation during subsequent remodeling. This mechanism distinguishes its potential wound-healing activity from interventions that primarily promote collagen deposition and may contribute to excessive scar formation under certain conditions.

3.2 Clinical data related to wound care

A 2022 review of controlled clinical trials reported that *Centella asiatica* may promote faster wound healing compared to control treatments. Beneficial effects were reported across several wound types, including burns, diabetic foot ulcers, hypertrophic scars, split-thickness skin grafts, and wounds following laser resurfacing. Improved healing was associated with enhanced collagen synthesis and extracellular matrix remodeling, consistent with findings from animal studies, as well as increased tensile strength of the healing tissue. However, the authors noted that a formal meta-analysis was not possible because of substantial heterogeneity in wound types, *C. asiatica* formulations, treatment protocols, and outcome measures across the included trials. Therefore, they emphasized the need for more standardized and adequately designed clinical studies before the magnitude and reliability of the treatment effect can be established.

Although much of the evidence on advanced delivery technologies remains at an early stage, a recent narrative review focusing on topical delivery methods reached a similar conclusion. Newer formulations, including hydrogels, nanostructured carriers, and microneedle systems, may enhance the skin penetration of triterpenoid glycosides. These delivery systems have also demonstrated accelerated wound closure in preclinical ulcer and burn models.

3.3 Cosmetic use and aging of the skin

An important piece of clinical evidence in the cosmeceutical field was provided by a network meta-analysis conducted by Kongkaew et al. (2020). The analysis included five blinded randomized trials involving 172 Asian women. Two trials reported a reduction in periorbital wrinkles after 12 weeks of treatment with a periocular gel and a cream. Two other trials compared *Centella asiatica* with tretinoin or *Pueraria mirifica*, with treatments applied to opposite sides of the face. The network meta-analysis indicated that *C. asiatica* was associated with greater wrinkle reduction than *P. mirifica* but less than tretinoin. In a comparative trial, *C. asiatica* was associated with fewer reported adverse events than tretinoin (10 vs. 35 events) and improved skin hydration than tretinoin. Another trial found that a lipstick containing asiaticoside reduced lip wrinkles over eight weeks, extending the evidence beyond the periorbital region [10]. The researchers suggested that *Centella asiatica* could represent a milder alternative to retinoid-based approaches for individuals seeking better tolerability, while emphasizing the need for longer-term safety data. They also highlighted the importance of consistent manufacturing and standardization of *C. asiatica* preparations. Overall, the cosmeceutical evidence appears promising, with a generally favorable short-term safety profile, but remains limited by the same standardization challenges identified throughout this review. In models of UVB-induced skin damage, asiaticoside and madecassoside have been reported to reduce reactive oxygen species and enhance endogenous antioxidant enzymes, including superoxide dismutase and catalase [11]. Flavonoids such as quercetin may also modulate signaling pathways including JAK/STAT3 and the IL-23/IL-17A axis, which are relevant to inflammatory and autoimmune skin conditions. These mechanisms extend beyond collagen synthesis. Although the number of clinical trials remains limited, research has advanced considerably in elucidating the mechanisms underlying the skin-specific effects of *C. asiatica* compared with earlier broad pharmacological surveys, as highlighted in a comprehensive 2025 review covering literature published from 2016 to 2025.

4. Microcirculatory and venous effects

The most developed clinical evidence for CA is in the management of chronic venous insufficiency (CVI), based primarily on a standardized preparation known as the total triterpenic fraction of CA (TTFCA). TTFCA has been extensively investigated by Italian vascular medicine researchers during the 1990s and 2000s. According to a 2013 systematic review that combined data from eight randomized controlled trials, TTFCA produced significant improvements in objective microcirculatory parameters, including transcutaneous partial pressures of carbon dioxide and oxygen, the rate of ankle swelling, and the venoarteriolar response, a reflex vasoconstriction measure that is frequently impaired in venous hypertension. Three of the eight included trials reported symptomatic improvements in leg heaviness, discomfort, and edema among treated individuals, although quantitative outcome data were not provided. The proposed mechanism focuses on the effects of triterpenoids on the connective tissue matrix of the venous wall, which contributes to the structural integrity of veins and may improve capillary filtration dynamics by promoting collagen synthesis in the vessel wall and surrounding perivascular connective tissue [12,13]. This mechanism is consistent with the collagen-modulating effects reported for *C. asiatica* in other tissues, although in this context, the proposed activity involves vascular rather than cutaneous connective tissue. The concordance between the proposed mechanism and reported clinical outcomes may help explain the continued investigation of TTFCA-based preparations in phlebology, although evidence for other therapeutic applications remains comparatively less developed. However, this evidence should be interpreted cautiously. A comprehensive 2020 Cochrane review of phlebotonic agents for venous insufficiency, including both plant- and non-plant-derived compounds, found that the overall quality of evidence for this therapeutic class was generally low to moderate, reflecting small trial sizes and inconsistent outcome reporting. These limitations are not specific to *C. asiatica*-derived preparations. TTFCA has also been reported to be well tolerated at doses of up to 180 mg/day for 12 months in trials investigating femoral and carotid plaque-related outcomes, according to the available literature [14].

5. Mood, Anxiety and Cognitive Function

5.1 Mechanisms of neuroprotection

There is a substantial body of preclinical evidence on the cognitive and neuroprotective effects of *Centella asiatica*, particularly from a research team that has extensively investigated a standardized water extract (CAW) in several rodent models of Alzheimer's disease and aging [15]. Long-term treatment with CAW enhances fear memory and object recognition, reduces amyloid- β plaque burden, and activates the NRF2-regulated

antioxidant response pathway in a 5xFAD transgenic mouse model of β -amyloid accumulation [16]. These findings build on earlier research showing that two weeks of treatment improved cognition and increased antioxidant gene expression without significantly altering plaque burden. In both wild-type and transgenic animals, CAW improved learning, memory, and executive function, reduced hippocampal mitochondrial dysfunction, and increased the expression of NRF2 and its antioxidant response element target genes in the hippocampus and cortex of the brain. Mechanistic evidence has expanded beyond antioxidant signaling, as metabolomic profiling of cortical tissue from treated 5xFAD mice also revealed modulation of brain-derived neurotrophic factor and upregulation of nicotinamide adenine dinucleotide (NAD^+), suggesting additional pathways through which CAW may exert its neuroprotective effects. Neuroblastoma cell lines were protected against both exogenous and endogenously generated β -amyloid toxicity using a phenolic-rich (rather than triterpenoid-rich) Gotu Kola water extract, but notably without anticholinesterase activity or protection against oxidative or glutamate-mediated damage. This highlights that "*Centella asiatica* extract" can refer to preparations with different active constituent profiles depending on the extraction solvent. Increased mitochondrial activity, enhanced phospholipase A2 inhibition, and neurotrophic effects on dendritic arborization and synaptogenesis mediated through ERK1/2 and Akt signal transduction are all attributed to neuroprotective effects in a more comprehensive phytochemistry-and-mechanism review that covers several in vitro models.

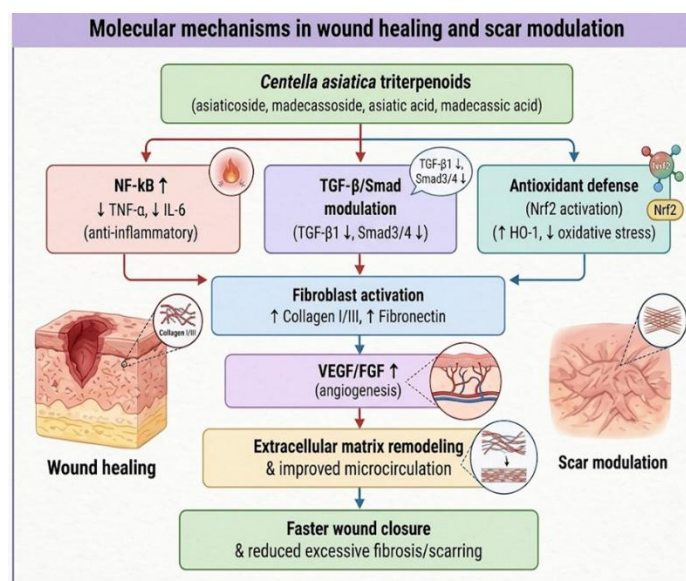


Figure3. Molecular mechanism of *Centella asiatica* in wound healing and scar modulation

5.2 A case study of clinical divergence in human cognitive experiments

Pooled data have not provided compelling evidence, and the available human evidence remains substantially weaker than that from preclinical rodent studies. Puttarak et al.'s 2017 systematic review and meta-analysis, which included five controlled trials of *Centella asiatica* alone and six studies of *C. asiatica*-containing combination products, remains an important synthesis of the available evidence. When cognitive outcomes were pooled across domains, *C. asiatica* did not differ significantly from the placebo in any of the investigated measures. Although the estimates were based on a small number of contributing trials and had relatively wide confidence intervals, the same analysis identified modest mood-related effects, including increased self-reported alertness (standardized mean difference [SMD] 0.71) and reduced anger scores one hour after dosing (SMD -0.81). Regarding methodological quality, 25% of the included studies were judged to have a high risk of bias, nearly two-thirds had an unclear risk of bias, and only one trial was assessed as having a low-risk of bias. Allocation concealment is also poorly described in the literature, highlighting important methodological limitations that should be considered when interpreting the available clinical evidence [17]. Despite some single-study results, individual trials show why the pooled outcome is null. A 750 mg daily dose for two months improved working memory. Increased the N100 component of event-related potentials along with self-reported mood improvement according to a double-blind placebo-controlled trial with 28 healthy elderly volunteers. However, the 250 mg dose showed no benefit, and the sample size was too small to support strong generalization [18]. Although it was primarily intended as a safety and exploratory efficacy study rather than a definitive efficacy trial, a phase 1 dose-ranging study of standardized aqueous extract (750 or 1000 mg daily) in 99 patients with post-stroke vascular cognitive impairment found the intervention safe and well tolerated compared to folate control over a six-week period. According to a recent update, a phase 1 randomized placebo-controlled trial of a standardized hot-water extract product is actively recruiting participants with mild cognitive impairment and early Alzheimer's disease with oxidative stress biomarkers and brain metabolite ratios as primary outcomes [19]. This design is notably focused on establishing target engagement and dose selection rather than powering a clinical efficacy claim, which is arguably the appropriate next step given the advancement of pharmacokinetic and preclinical mechanistic work ahead of clinical dose-finding [20]. The null findings from human analyses differ from those observed in rodent studies; however, this discrepancy does not necessarily indicate that the underlying biological mechanisms are invalid or non-existent in humans. When allometric

scaling and the low oral bioavailability of parent triterpenoid glycosides in humans are considered, the findings may reflect differences in systemic exposure relative to the doses shown to be effective in rodents. This possibility may be further influenced by short treatment durations, small sample sizes, and the use of outcome measures that are not closely aligned with the cognitive domains predicted to be most responsive to the proposed mechanisms, particularly executive functioning and hippocampal-dependent memory rather than global cognitive screening scores. An informed dose-ranging trial, similar to the one currently underway in moderate cognitive impairment, is necessary to address this issue, which can be tested [21].

5.3 Anxiolytic effects

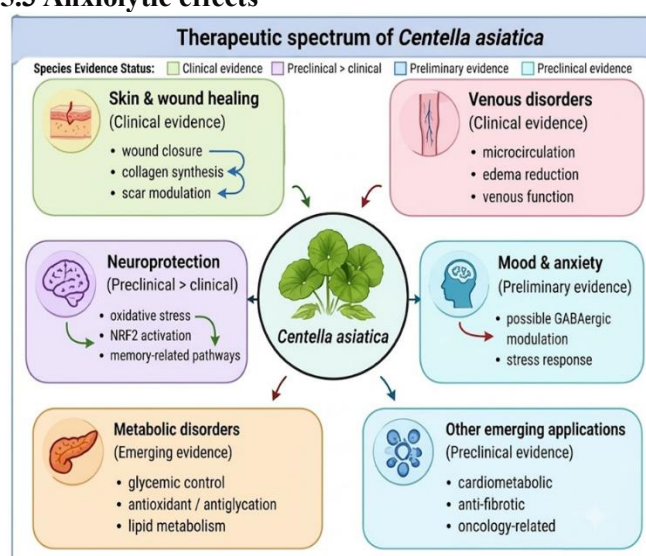


Figure 4. Therapeutic spectrum of *Centella asiatica* with levels of evidence and process connections.

Although the anxiolytic literature on *Centella asiatica* is limited, it includes relatively specific and directly testable results. Following rodent studies showing that *C. asiatica* reduced locomotor activity, improved maze performance, and attenuated responses to acoustic stimuli, Bradwejn et al. administered a 12-g dose of dried *C. asiatica* to healthy participants in a double-blind, placebo-controlled study. The treatment was associated with a reduction in the startle response, which is a well-established experimental measure of anxiety in mice. Preclinical research suggests that *C. asiatica* may enhance the activity of enzymes involved in GABA synthesis, providing a possible basis for the modulation of GABAergic signaling. However, this does not establish that *C. asiatica* has anxiolytic effects in humans. In contrast to the Bradwejn startle-response study, another small clinical study in patients with anxiety disorders reported reductions in anxiety and associated depressive symptoms on standardized psychological rating scales. However, the methodological

details of this trial are less rigorously documented in the secondary literature, and its findings should, therefore, be regarded as preliminary rather than as confirmatory. Taken together, the available anxiolytic evidence is suggestive but limited to short-term or acute exposure in small sample sizes. Virtually no clinical trial evidence currently addresses sustained anxiolytic efficacy over several weeks to months, which represents a clinically relevant timeframe for the management of anxiety disorders [22].

6. Metabolic and Additional New Uses

6.1 Diabetes complications and glycemic management

Recently, research on the role of *C. asiatica* in metabolic diseases has progressed from laboratory investigations to human clinical trials. The emerging evidence suggests a potentially supportive role rather than a clearly disease-modifying effect. In a 2025 randomized, double-blind, placebo-controlled study conducted in Thailand, 70 patients with type 2 diabetes received either 1200 mg/day of *C. asiatica* extract or placebo for six months. The primary outcome was glycated hemoglobin (HbA1c), while secondary outcomes included fasting blood glucose, LDL cholesterol, and treatment-related adverse effects [23]. Even though this is one of the best-designed metabolic trials for the plant far it does not provide enough proof to match the evidence from the venous-insufficiency trial. In another three-arm randomized trial with 159 people who had type 2 diabetes and dry skin a combination of oral and topical *C. asiatica* was compared to a placebo. The results showed reductions in advanced glycation end-products (carboxymethyl-lysine) lower IL-1 α and higher superoxide dismutase activity in the skin. This study sits at the crossroads of *C. asiatica*'s skin and metabolic actions. Preclinical studies explain *C. asiatica*'s anti-high-blood-sugar effect by improving insulin sensitivity and lowering glycation stress, which matches the antioxidant findings in other drug studies.

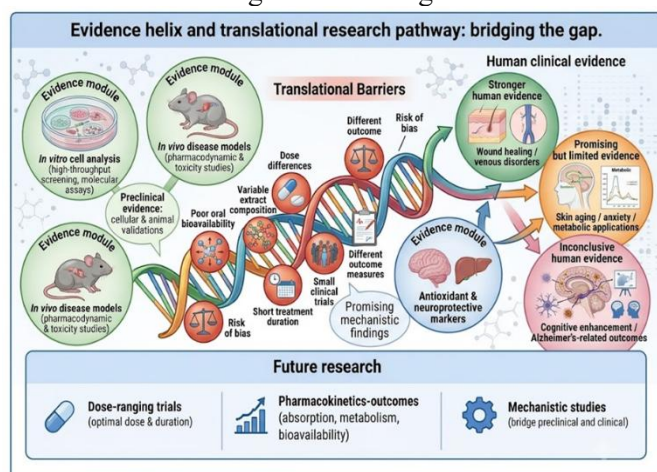


Figure5. Preclinical- clinical evidence gap and future research pathway

6.2 Neuroprotection beyond Alheimers disease and oncology-adjacent discoveries

Asiatic acid, a component of *Centella asiatica*, has a broad preclinical record that extends beyond the field of Alzheimer's disease research. It has shown activity in models of Parkinson's disease, obesity, high blood pressure, heart attack injury, atherosclerosis, liver and lung scarring, and several cancers, including liver, lung, and ovarian cancer. Asiatic acid reduces cytokine levels, stops collagen build-up, shrinks tumor size and spread, and raises cell death markers such as caspase-9 and caspase-3 in lung scarring and lung cancer models. These findings also explain why a long list of disease models does not automatically mean clinical benefit; almost no cancer or heart metabolism studies have been tested in controlled human trials, and this review deliberately avoids turning a list of laboratory results into a treatment menu [24].

7. Adverse Effects, Safety and Tolerance

Centella asiatica is generally well-tolerated when used appropriately, according to available clinical and safety reports. The plant is also consumed as a vegetable in some parts of South and Southeast Asia, with reported dietary use of approximately 0.5–1.5 g of dried leaves. The Botanical Safety Handbook classifies *C. asiatica* as Class 1 herb, indicating that it is generally considered safe when used appropriately and according to recommended conditions of use. Reported adverse effects in clinical studies include gastrointestinal discomfort, flatulence, nausea, headache, decreased appetite, fatigue, and occasional skin rash. In some combination-product trials, the incidence of these adverse effects was similar to or lower than that reported with placebo. The main safety concern requiring attention is rare acute liver injury. Three women aged 49–61 years developed jaundice after taking *Centella asiatica* preparations for weight loss for 20–60 days [25]. Their liver enzymes were markedly elevated, with alanine aminotransferase (ALT) concentrations reaching 1694 U/L in one case. Liver biopsies demonstrated different patterns of hepatitis, including granulomatous hepatitis with marked necrosis and apoptosis and chronic hepatitis with cirrhotic transformation and intense neuroinflammatory activity. All three patients improved after discontinuation of the herbal product, although one experienced recurrence following re-exposure. The U.S. National Institutes of Health Liver Tox database identifies *C. asiatica* as a probable but rare cause of clinically apparent acute liver injury with jaundice. Available small controlled trials have generally not demonstrated significant liver enzyme elevations during short-term use; however, the number of studies reporting systematic liver function monitoring is limited. Liver Tox also notes that the composition of the products involved in published hepatotoxicity cases was

not always adequately characterized, leaving the possibility of contamination or other hepatotoxic constituents open.

Overall, the available evidence is more consistent with a rare, potentially idiosyncratic hepatotoxic reaction than with a clearly established dose- or duration-dependent toxicity profile. Therefore, caution is warranted with high-dose or prolonged oral use, particularly when the product composition is unknown. Individuals who develop symptoms suggestive of liver injury, such as jaundice or dark urine, should discontinue using the product and undergo appropriate medical evaluation.

Despite the widespread use of *Centella asiatica* in dietary supplements, the U.S. Food and Drug Administration's CFSAN Adverse Event Reporting System has not identified a clear signal of harm associated with its use. Although this finding is reassuring, the absence of a detected signal does not exclude rare or underreported adverse events from occurring. Allergic cutaneous reactions have also been reported, although these appear to be relatively uncommon and are generally described as manageable after discontinuation of the preparation.

or exposure to active constituents or a genuine lack of efficacy of the intervention itself.

- Poor and variable oral absorption of drugs. Oral doses taken directly from rodent injection studies rely on unreliable data because the parent glycosides are barely absorbed. This activity is derived from the acid metabolites produced by the gut and liver, which likely vary with each person's gut bacteria.

- Short treatment. Small sample sizes. Treatments are usually measured in weeks, not months or years, which would matter for problems such as cognitive decline or generalized anxiety, and trials rarely involve more than a few dozen to a few hundred participants across cognitive, anxiety, and most metabolic studies [26].

- Outcome measures that may not fit the science of the study. This is especially true in trials: broad screening tools may not match the specific hippocampal and prefrontal brain areas that preclinical research suggests should respond best to treatment, thus hiding a real but domain-specific effect.

- Bias concerns in trials. A formal risk-of-bias review of studies found that most had unclear or high risk of bias, mainly because of poor reporting of allocation concealment and randomization. This pattern probably extends to areas where a thorough bias review has not yet been conducted.

- Species and route gaps. Much of *C. asiatica*'s mechanisms come from models that use routes and doses (often intraperitoneal or high-dose oral gavage) that do not match what humans can safely take orally. This review highlights these gaps wherever it appears. This is especially true for oncology-adjacent and several heart metabolism applications.

9. Research Deficits and Prospects

- First, pharmacokinetically anchored dose-ranging trials are required for mood and cognitive outcomes. In these trials, dosing was determined by the target plasma concentrations of madecassic acid and asiatic acid, the metabolites that are now known to be the predominant circulating species following oral dosing, rather than by historical conventions [27]. This strategy is modeled by phase 1 pharmacokinetic and target-engagement research currently being conducted in mild cognitive impairment, and after dose selection is verified, it should be expanded to a suitably powered efficacy trial.

Second, rather than using global screening tools, whose insensitivity may partially account for the null meta-analytic result to date, cognitive outcome measures in subsequent trials should be chosen to match the specific domains implicated by rodent mechanistic work, particularly executive function and hippocampal-dependent memory [28]. Cognitive testing combined with biomarkers already validated in the phase 1 human pharmacokinetic study, such as peripheral blood NRF2-

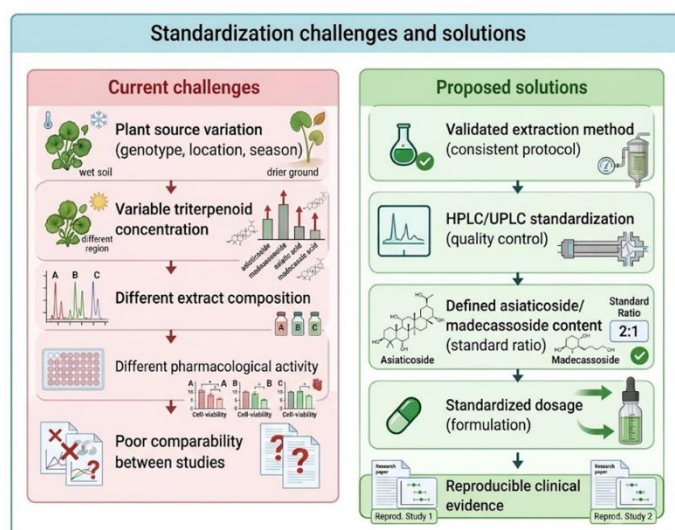


Figure 6. Detailed standardization challenges and proposed solutions for *Centella asiatica* extracts and formulations

8. Present Restraints and Difficulties

- No standard extract. Most *Centella asiatica* studies, with notable exceptions such as ECa 233 and TTFCA, do not report validated quantitative analyses of triterpenoid content in the used preparations. This lack of phytochemical standardization makes meaningful comparisons across trials difficult and may contribute to the variability in the observed outcomes. This also complicates the interpretation of null findings in cognitive function meta-analyses, as it is often unclear whether the absence of a significant effect reflects an insufficient dose

pathway gene expression, would enable a trial to show target engagement even if the clinical effect size turns out to be modest and would help distinguish "wrong dose" from "wrong mechanism" as an explanation for any subsequent null result [29].

- Third, although the dermatological and venous insufficiency literature is relatively mature, it would benefit from head-to-head trials using standardized extracts at defined triterpenoid dosing against current standard-of-care comparators (such as compression therapy for CVI or standard retinoid regimens for photoaging). This is because most of the evidence currently available compares *Centella asiatica* to a placebo rather than to the treatments patients would otherwise receive [30,31].

- Fourth, rather than depending just on a few older case reports, the hepatotoxicity signal merits rigorous pharmacovigilance attention. To determine if risk is truly idiosyncratic or concentrated in recognized higher-risk regimens or populations, a prospective registry or systematic adverse-event capture within ongoing and future studies, stratified by dose, duration, and concurrent hepatotoxic exposures, might be helpful [32].

Fifth, early phase human trials, even small biomarker-driven phase 1/2 studies rather than large efficacy trials, would help determine which of these numerous preclinical signals are worth pursuing clinically, given the extensive preclinical footprint of asiatic acid in oncology and cardiometabolic models. Currently, the entire non-dermatological, non-venous, and non-cognitive aspects of the plant's pharmacological reputation rest solely on preclinical data [33,34].

10. Conclusion

Centella asiatica has multiple therapeutic stories with varying degrees of evidentiary maturity, all of which are connected by a common and increasingly well-characterized chemical composition. Despite concerns about standardization, the plant has earned a fairly solid place in dermatological and phlebological practice, where the mechanism is local and structural, such as collagen synthesis and connective tissue remodeling in the skin and venous walls. Clinical trials have largely confirmed the predictions made using these cell and animal models. The most economical explanation is not that the biology is incorrect, but rather that dosing, trial duration, and outcome selection have not yet been calibrated to the knowledge of the compound's poor and metabolite-dependent oral bioavailability. In cases where the desired effect is centrally mediated and diffuse, cognition above all, an exceptionally rich preclinical literature has not yet been matched by convincing human trial data. A real, albeit rare, hepatotoxic signal that supports monitoring during protracted high-dose usage rather than raising concerns about regular dietary or short-term therapeutic

exposure tempers the perceived safety for normal short-term use. Instead of merely adding more preclinical disease models, future research would be more beneficial if it focused on the pharmacokinetic and trial design gaps found in this study. The chemistry and preclinical mechanisms are, for the most part, already fairly well understood; the current challenge is to determine which of these mechanisms produce significant effects in humans, at what dose, and in which population.

Author Contributions

Deepti Dwivedi: Conceptualization, literature review, data collection and analysis, manuscript preparation.

Himanshu: Literature search, data interpretation, and critical revision of the manuscript.

Ankur Srivastava: Supervision, validation, critical evaluation, and final approval of the manuscript.

All the authors have read and approved the final version of the manuscript.

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