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Review Article

Centella asiatica in Stress-Induced Depression: Multitarget Modulation of Neuroendocrine, Inflammatory, Redox, and Neuroplastic Pathways

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Abstract

Chronic stress is a major etiological factor in depression and is characterized by dysregulation of the hypothalamic pituitary adrenal axis, neuroinflammation, oxidative imbalance, and impaired neuroplasticity. Centella asiatica has gained attention as a potential natural neuromodulator; however, its mechanistic role in stress induced depression has not been comprehensively synthesized. This narrative review integrates preclinical and selected clinical evidence published between 2016 and 2026 to evaluate the antidepressant related mechanisms of Centella asiatica and its principal triterpenoids. Across validated stress models, administration of Centella asiatica consistently attenuated HPA axis hyperactivity, restored hippocampal brain derived neurotrophic factor signaling, suppressed NF kappa B mediated neuroinflammation, enhanced endogenous antioxidant defenses, and reduced ferroptosis associated neuronal injury. These molecular and cellular adaptations were accompanied by reproducible improvements in depressive like behaviors and preservation of hippocampal structural integrity. Emerging evidence also suggests involvement of the microbiota gut brain axis. Overall, the findings support a multitarget neuromodulatory profile consistent with contemporary multifactorial models of depression. Well designed biomarker driven clinical trials are warranted to confirm translational relevance and therapeutic potential in human populations.

Keywords: Centella asiatica; stress induced depression; HPA axis; oxidative stress; neuroplasticity

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1 Introduction

Chronic stress is widely recognized as a major etiological factor in the development of depression. Prolonged exposure to stress leads to hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in sustained elevation of glucocorticoids, including cortisol in humans and corticosterone in experimental animals [1], [2]. Persistent activation of the HPA axis disrupts its negative feedback regulation and promotes long-term glucocorticoid overexposure. This condition contributes to neuronal toxicity, impaired neuroplasticity, and reduced expression of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus and prefrontal cortex, which play central roles in mood regulation, memory, and executive function [3], [4]. These structural and molecular alterations form a key biological basis linking chronic stress to major depressive disorder [1], [2].

In addition to the classical monoamine hypothesis, contemporary models of depression increasingly emphasize the roles of neuroinflammation and oxidative stress. Elevated levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha are associated with activation of the nuclear factor kappa B signaling pathway, which suppresses BDNF transcription and increases neuronal vulnerability to oxidative damage [2]. Excessive accumulation of reactive oxygen species further accelerates mitochondrial dysfunction and disrupts synaptic transmission. Depression is therefore understood as a multifactorial neurobiological disorder arising from the interaction among HPA axis dysregulation, neuroinflammation, oxidative imbalance, and impaired neuroplasticity [1], [2].

Although selective serotonin reuptake inhibitors are widely prescribed as first-line antidepressants, important limitations remain. The onset of therapeutic effect is relatively delayed, typically requiring four to six weeks to achieve full clinical benefit [5], [6]. Systemic adverse effects, including sexual dysfunction, gastrointestinal disturbances, sleep disruption, and weight gain, frequently compromise long-term adherence. Regulatory agencies such as the United States Food and Drug Administration have issued black box warnings regarding increased risk of suicidality in children, adolescents, and young adults aged 18 to 24 years [5], [6]. Moreover, treatment response is heterogeneous, and a substantial proportion of patients fail to achieve meaningful remission [5]. These therapeutic challenges highlight the need for alternative or adjunctive neuromodulatory agents with multitarget mechanisms that address inflammatory, oxidative, and neurotrophic pathways simultaneously [2], [6].

In this context, Centella asiatica, commonly known as Gotu kola, has gained attention as a potential natural neuromodulator. The plant has long been used in traditional Chinese medicine, Ayurveda, and Southeast Asian ethnomedicine to enhance cognitive function and promote nervous system balance [3], [6], [7]. Its principal bioactive constituents, particularly pentacyclic triterpenoids such as asiaticoside, madecassoside, asiatic acid, and madecassic acid, demonstrate neuroprotective, antioxidant, and anti-inflammatory properties in various experimental models [3], [4], [6].

Preclinical studies using stress-based depression models, including chronic unpredictable mild stress and restraint stress paradigms, have shown that administration of Centella asiatica extract reduces depressive-like behaviors and normalizes serum corticosterone levels [4]. These endocrine changes are accompanied by increased BDNF expression in the hippocampus and prefrontal cortex, as well as improvements in synaptic density. Activation of the nuclear factor erythroid 2 related factor 2 pathway has also been reported, leading to enhanced transcription of cytoprotective genes such as heme oxygenase 1 and reduced accumulation of reactive oxygen species, thereby mitigating stress-induced neuronal damage [2], [3].

Several double blind clinical trials further suggest that Centella asiatica extract may reduce anxiety scores and attenuate physiological stress responses in healthy individuals exposed to acute psychological stressors. However, variability in dosage regimens, extract standardization, and outcome measures, particularly the limited integration of biomolecular markers, has constrained a comprehensive mechanistic understanding of its antidepressant potential [7].

To date, no review has comprehensively synthesized empirical evidence regarding the role of Centella asiatica in modulating HPA axis activity while simultaneously restoring neuroplasticity in stress induced depression. Therefore, this review aims to systematically synthesize and critically evaluate

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current preclinical and clinical findings on the potential of Centella asiatica as a natural antidepressant agent within the framework of HPA axis dysregulation, oxidative stress, neuroinflammation, and impaired neuroplasticity.

2 Method

2.1 Study Design

This study was conducted as a narrative literature review aimed at synthesizing current evidence regarding the mechanistic role of Centella asiatica in stress-induced depressive pathophysiology. The review focuses on integrating experimental findings related to hypothalamic–pituitary–adrenal (HPA) axis dysregulation, neuroinflammation, oxidative stress, and impaired neuroplasticity. A narrative approach was selected to allow in-depth conceptual integration of complex biological pathways. Although a full systematic review protocol was not implemented, structured search and selection procedures were applied to enhance transparency and methodological consistency.

2.2 Literature Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, and Google Scholar for studies published between January 2016 and January 2026. This time frame was selected to capture contemporary mechanistic developments within the last decade. The search strategy employed Boolean operators using the following combined syntax: ("Centella asiatica" OR "asiaticoside" OR "madecassoside" OR "asiatic acid") AND ("depression" OR "depressive-like behavior" OR "chronic stress" OR "CUMS" OR "restraint stress") AND ("HPA axis" OR "corticosterone" OR "BDNF" OR "neuroinflammation" OR "oxidative stress" OR "Nrf2" OR "NF-kB"). For Google Scholar, screening was limited to the first 200 most relevant results based on title and abstract relevance. In addition, reference lists of eligible articles were manually examined to identify further pertinent studies.

2.3 Eligibility Criteria

Studies were included if they met the following criteria:

- Original research articles published in peer-reviewed journals between 2016 and 2026.
- *In vivo* or *in vitro* studies evaluating *Centella asiatica* or its major bioactive constituents.
- Use of validated experimental models of stress-induced depressive-like behavior or cognitive impairment, including but not limited to Chronic Unpredictable Mild Stress (CUMS), restraint stress, maternal deprivation, sleep deprivation, or forced swim/tail suspension tests.
- Reporting of behavioral outcomes together with at least one molecular or biochemical endpoint related to HPA axis activity, BDNF expression, inflammatory mediators, or oxidative stress markers.

Review articles, editorials, conference abstracts without primary data, and non-peer-reviewed publications were excluded.

2.4 Study Selection

The literature search was conducted across three electronic databases: Scopus, PubMed, and Google Scholar. The initial search identified 58 records from Scopus, of which 49 met the predefined publication year range (2016–2026). PubMed yielded 15 records that were already consistent with the specified year and article-type criteria. The Google Scholar search initially retrieved 2,450 records; after restricting the publication period to 2016–2026, 2,120 records remained. Given the large number of results, screening from Google Scholar was limited to the first 200 articles ranked by relevance based on title and abstract evaluation.

In total, 264 records were identified (Scopus = 49; PubMed = 15; Google Scholar = 200). After removing duplicate records (n = 53), 211 unique studies remained for title and abstract screening.

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During the initial screening phase, 176 records were excluded because they did not meet the predefined inclusion criteria. The primary reasons for exclusion included the absence of validated stress-induced depressive models, lack of behavioral assessment, or failure to report relevant molecular or biochemical endpoints. Subsequently, 35 full-text articles were assessed for eligibility. Of these, 25 were excluded due to the absence of molecular endpoints (n = 9), lack of behavioral assessment (n = 6), classification as review articles (n = 5), or use of inadequate stress models (n = 5). Ultimately, ten studies fulfilled all inclusion criteria and were included in the qualitative synthesis.

2.5 Data Extraction and Synthesis

Relevant data from the ten included studies were extracted using a structured matrix. The extracted variables included: study author and year, experimental stress model and behavioral tests utilized, details of the intervention (type of extract or compound, dose, route of administration, and duration), comparator or positive control (e.g., standard antidepressants), molecular and biochemical endpoints measured, and the main findings. Findings were synthesized thematically into principal mechanistic domains: HPA axis modulation, neuroplasticity and BDNF regulation, attenuation of neuroinflammatory pathways, and reduction of oxidative stress. The synthesis emphasized mechanistic convergence rather than quantitative effect size estimation.

2.6 Methodological Considerations

Although formal risk-of-bias assessment tools were not applied due to the narrative design, methodological robustness was critically evaluated based on experimental clarity, adequacy of control groups, validation of behavioral paradigms, and completeness of molecular outcome reporting. Studies with limited methodological transparency were interpreted cautiously within the overall synthesis.

3 Result and Discussion

The ten included experimental studies consistently demonstrated that Centella asiatica and its principal triterpenoids exert antidepressant-like and neuroprotective effects across diverse validated stress paradigms. Despite heterogeneity in stress induction methods, doses, and experimental duration, the direction of outcomes was remarkably consistent: behavioral recovery was paralleled by normalization of neuroendocrine, inflammatory, oxidative, and neurotrophic markers. A structured summary of the included studies is presented in Table 1.

Table 1. Summary of Included Experimental Studies on Centella asiatica in Stress-Induced Depression Models

Study	Stress Model & Behavioral Tests	Intervention (Dose; Route; Duration)	Comparator	Molecular / Biochemical Endpoints	Main Findings
Ren et al., 2024 [8]	CUMS (7 weeks); SPT, FST, OFT	Asiaticoside 10, 20, 40 mg/kg p.o. (4 weeks)	Fluoxetine 20 mg/kg p.o.	CRH; CORT; BDNF; 5-HT1A; IL-6; TNF-α; IL-10; serum 5-HT; gut microbiota; SCFAs	Reversed depressive-like behavior; normalized CRH and CORT; increased BDNF and 5-HT1A; reduced pro-inflammatory cytokines; restored gut microbiota composition and SCFAs.

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Wang et al., 2020 [9]	CUMS (4 weeks); SPT, FST, TST	Asiaticoside 20, 40 mg/kg p.o.	–	TNF-α; IL-1β; IL-6; p-NF-κB; NLRP3; caspase-1; cAMP; PKA; p-CREB; BDNF; 5-HT; NE	Reduced immobility time; suppressed NF-κB/NLRP3 activation; increased cAMP/PKA/p-CREB signaling; restored BDNF and monoamine levels.
Zhou et al., 2025 [10]	Chronic restraint stress (4 weeks); SPT, FST	Asiaticoside 20 mg/kg p.o. (28 days)	–	BDNF; p-TrkB; PSD95; DCX; Nrf2; GPX4; SLC7A11; iron load; Iba1; TEM	Attenuated depressive behavior; inhibited hippocampal ferroptosis; activated BDNF/Nrf2/GPX4 pathway; reduced iron accumulation and microglial activation; preserved synaptic structure.
Bertollo et al., 2024 [11]	Maternal deprivation; FST	Hydroalcoholic extract 30 mg/kg p.o.; Madecassic acid 10 mg/kg p.o.	Escitalopram 10 mg/kg p.o.	TBARS; IL-1β; IL-6; TNF-α	Reduced immobility time; decreased lipid peroxidation and pro-inflammatory cytokines; comparable behavioral improvement to escitalopram.
Jagadeesan et al., 2024 [12]	CUMS (64 days)	Crude extract 200, 400, 800 mg/kg p.o.	Fluoxetine 10 mg/kg	CAT mRNA; AChE; hippocampal neuron density	Improved behavioral outcomes; increased catalase expression; normalized AChE activity; prevented hippocampal neuronal loss in a dose-dependent manner.
Rochmah et al., 2019 [13]	Chronic stress (28 days)	Ethanolic extract 150, 300, 600 mg/kg p.o.	–	TNF-α; IL-10; BDNF; SIRT1	Reduced TNF-α; increased IL-10 and BDNF levels; improved stress-related behavioral parameters independent of SIRT1 modulation.
Sari et al., 2019 [14]	Chronic electrical stress; Morris Water Maze	Ethanolic extract 150, 300, 600 mg/kg p.o.	–	BDNF mRNA; TrkB; ERK1/2	Improved cognitive performance; upregulated BDNF/TrkB/ERK1/2 signaling in hippocampus.

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Chanana & Kumar, 2016 [15]	Sleep deprivation (72 h); EPM	Extract 150, 300 mg/kg p.o. (8 days)	–	MDA; GSH; SOD; Catalase; TNF-α; NO	Reduced anxiety-like behavior; decreased MDA and TNF-α; increased antioxidant enzyme levels; NO-dependent neuroprotective effect.
Padmiswari et al., 2025 [16]	Chronic immobilization stress (14 days); histological analysis	Ethanolic leaf extract 100, 200, 300 mg/kg p.o. (30 days)	Vitamin E 100 mg/kg p.o.	Hippocampal neuron count (CA1, DG); brain weight; phytochemical profile; IC_{50} (DPPH)	Increased brain weight and hippocampal neuron number in a dose-dependent manner; demonstrated strong antioxidant activity (IC_{50} 47.2 µg/mL); neuroprotective against stress-induced neuronal loss.
Poleszak et al., 2025 [17]	FST, TST (Albino Swiss mice)	Asiatic acid 5 mg/kg i.p. + Imipramine 15 mg/kg; Reboxetine 2.5 mg/kg; Escitalopram 2 mg/kg	Antidepressants alone	Catalase; GPx; TBARS; drug serum/brain levels	Sub-effective asiatic acid potentiated antidepressant activity without altering drug pharmacokinetics; increased catalase and GPx; reduced TBARS; enhanced pharmacodynamic antidepressant response.

As shown in Table 1, most studies employed chronic unpredictable mild stress (CUMS) or chronic restraint stress models, both widely recognized for mimicking human stress-related depressive phenotypes. Behavioral outcomes were primarily assessed using sucrose preference, forced swimming, tail suspension, open field, and Morris water maze tests.

Interventions ranged from crude and ethanolic extracts to purified compounds such as asiaticoside, madecassic acid, and asiatic acid. Doses varied substantially; however, a dose-dependent trend was evident in several studies. Importantly, all studies incorporated at least one molecular or biochemical endpoint, enabling mechanistic interpretation beyond behavioral observation.

Biomarkers clustered into four principal domains:

- HPA axis regulation
- Neuroplasticity signaling (BDNF-related pathways)
- Neuroinflammation
- Oxidative stress and ferroptosis
- This convergence forms the foundation for the integrative discussion below.

3.1 HPA Axis Regulation and Stress Adaptation

Chronic stress exposure led to elevated corticotropin-releasing hormone (CRH) and corticosterone levels in CUMS models. Oral asiaticoside administration normalized CRH and corticosterone concentrations while reversing depressive-like behavior [8]. Given that sustained glucocorticoid elevation impairs hippocampal neurogenesis and suppresses BDNF transcription, restoration of HPA axis balance suggests that Centella asiatica acts at an upstream regulatory level of stress physiology. This distinguishes it mechanistically from monoamine-focused pharmacotherapy, which primarily targets synaptic neurotransmission [13], [14]

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3.2 Restoration of Neuroplasticity Through BDNF Signaling

Reduced hippocampal BDNF expression is a central feature of stress-induced depression. Several studies demonstrated significant upregulation of BDNF following treatment with Centella asiatica extracts or asiaticoside [10], [14], [18].

Activation of the cAMP/PKA/p-CREB pathway was shown to mediate BDNF transcriptional enhancement [18]. In addition, phosphorylation of TrkB and downstream ERK1/2 signaling was significantly increased, correlating with improved memory performance and synaptic integrity [10], [14]. Notably, asiaticoside also increased hippocampal 5-HT and norepinephrine concentrations [18], suggesting an interaction between neurotrophic and monoaminergic systems rather than exclusive dependence on either mechanism.

3.4 Anti-Inflammatory Modulation: NF-κB and NLRP3

Chronic stress elevated TNF-α, IL-1β, and IL-6 levels in hippocampal tissue. Asiaticoside significantly suppressed these cytokines while inhibiting NF-κB phosphorylation and NLRP3 inflammasome activation [18]. In a maternal deprivation model, both hydroalcoholic extract and madecassic acid reduced lipid peroxidation and pro-inflammatory cytokine levels [11]. Interestingly, reduced TNF-α did not directly predict increased BDNF in regression analysis, indicating partially independent but convergent mechanisms [13]. This suggests that anti-inflammatory and neurotrophic effects may operate in parallel rather than through a single linear cascade.

3.4 Oxidative Stress and Ferroptosis Inhibition

Oxidative imbalance was a consistent pathological finding. Extract administration increased catalase expression, restored AChE activity, and prevented hippocampal neuronal loss in CUMS rats [12]. Sleep deprivation models also demonstrated reduced MDA levels and improved antioxidant enzyme activity following treatment [15]. More recently, asiaticoside was shown to activate the BDNF/Nrf2/GPX4 pathway and reduce iron accumulation in the hippocampal CA1 region, thereby inhibiting ferroptosis [10]. The identification of ferroptosis modulation is particularly relevant, as iron-dependent lipid peroxidation has emerged as a novel contributor to depressive pathology. This mechanistic layer extends beyond classical oxidative stress models and positions Centella asiatica within emerging cell-death regulatory frameworks [19].

3.5 Structural Neuroprotection

Histological findings provide an additional layer of validation for the molecular and behavioral outcomes discussed previously. In a chronic immobilization stress model, administration of ethanolic leaf extract of Centella asiatica significantly increased brain weight and hippocampal neuronal density in the CA1 region and dentate gyrus in a dose-dependent manner compared with untreated stressed controls [16]. The reduction in neuronal number observed in the stress group reflects the neurotoxic consequences of sustained glucocorticoid exposure and oxidative stress, both of which critically impair hippocampal integrity a brain region highly vulnerable to persistent activation of the HPA axis [20], [21].

The restoration of neuronal density following intervention indicates that the effects of C. asiatica extend beyond modulation of inflammatory and oxidative biomarkers, encompassing preservation of structural neural integrity. Biologically, this morphological protection is consistent with activation of the BDNF/TrkB signaling pathway and enhancement of endogenous antioxidant defenses, as previously reported [12], [14]. Thus, structural preservation can be interpreted as a downstream manifestation of integrated molecular modulation.

Importantly, histological evidence helps exclude the possibility that behavioral improvements are merely attributable to enhanced locomotor activity or nonspecific psychostimulant effects. The observed concordance between neuronal structural recovery and normalization of biochemical parameters supports

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the interpretation that behavioral amelioration reflects genuine restoration of hippocampal circuit function rather than transient enhancement of task performance [22].

3.6 Microbiota Gut Brain Axis

A broader mechanistic dimension emerges from studies examining the involvement of the microbiota gut brain axis. In a chronic unpredictable mild stress (CUMS) model, asiaticoside not only ameliorated depressive-like behaviors but also partially restored gut microbial community structure and short-chain fatty acid (SCFA) concentrations particularly acetate, propionate, and butyrate [8]. These microbial and metabolic shifts were accompanied by normalization of corticotropin-releasing hormone (CRH) and corticosterone levels, as well as upregulation of hippocampal BDNF and 5-HT1A receptor expression [23], [24].

Conceptually, these findings expand the mechanistic framework of Centella asiatica beyond purely central actions toward systemic regulatory effects. SCFAs are known to influence blood brain barrier permeability, microglial activation states, and neurotransmitter synthesis, thereby exerting both direct and indirect effects on neuroplasticity and central inflammatory signaling. Modulation of gut microbial composition, therefore, may serve as an upstream regulator of hippocampal function and stress responsivity [25].

Importantly, these data suggest that the antidepressant-like effects of asiaticoside are unlikely to depend solely on central nervous system penetration of active compounds. Rather, its efficacy may also derive from its capacity to reprogram the peripheral immunometabolic milieu. This positions C. asiatica within an emerging therapeutic paradigm centered on host microbiome interaction, a systems-level approach that is gaining increasing recognition in contemporary models of depressive pathophysiology [8], [10].

3.7 Adjunctive Potential

The potential of Centella asiatica derived compounds as adjunctive therapy is further supported by evidence demonstrating that sub-effective doses of asiatic acid significantly enhanced the antidepressant-like activity of imipramine, reboxetine, and escitalopram in animal models, without altering drug concentrations in serum or brain tissue. The absence of pharmacokinetic changes indicates that the interaction is pharmacodynamic in nature, rather than attributable to increased drug bioavailability or altered distribution [17].

This synergistic effect was accompanied by increased catalase and glutathione peroxidase activity, along with reduced thiobarbituric acid reactive substances (TBARS), reflecting improved antioxidant capacity in brain tissue [17]. These findings support the hypothesis that oxidative stress may constrain responsiveness to monoaminergic antidepressants and that modulation of redox pathways can potentiate the therapeutic efficacy of conventional agents.

Clinically, these observations are particularly relevant in the context of partial responders and treatment-resistant depression. A multimodal strategy targeting monoaminergic transmission, neuroinflammation, and oxidative stress simultaneously may yield more stable and comprehensive therapeutic outcomes than monotherapy alone. Nonetheless, translational validation remains essential. Carefully designed, biomarker-driven randomized controlled trials are required to confirm the safety, mechanistic coherence, and clinical effectiveness of such combination approaches in human populations.

4. Conclusion

This narrative review demonstrates that Centella asiatica possesses a coherent and biologically plausible antidepressant profile within stress-induced depression models. Across diverse experimental paradigms, its administration consistently attenuated HPA axis hyperactivation, restored hippocampal BDNF-mediated neuroplasticity, suppressed NF-κB–driven neuroinflammation, enhanced antioxidant defenses, and limited ferroptosis-associated neuronal injury. These molecular and cellular adaptations were accompanied by reproducible behavioral improvement and, in several studies, preservation of hippocampal structural integrity.

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Taken together, the evidence positions Centella asiatica as a multitarget neuromodulatory candidate aligned with contemporary pathophysiological models of depression that emphasize stress-driven network dysregulation rather than isolated monoamine deficiency. While preclinical findings are robust, clinical translation requires rigorously standardized extracts and biomarker-integrated randomized controlled trials to confirm safety, mechanistic validity, and therapeutic efficacy in human populations.

5. Declarations

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5.2 Author contributions

Onny Ziasti Fricillia designed the study framework, supervised the conceptual development, and led the drafting and critical revision of the manuscript. Victoria Yulita F contributed to the comprehensive literature review, data extraction, and synthesis of findings on the neuroendocrine and inflammatory modulation of Centella asiatica in stress-induced depression. Muh. Deni Kurniawan provided analytical support, validated the redox and neuroplasticity sections, and reviewed methodological consistency throughout the manuscript. Difatya Mula Hardianto as student contributor assisted in compiling additional references, organizing data tables, and formatting the manuscript for submission. All authors discussed the results, contributed to the interpretation of findings, and approved the final version of the article.

5.3 Ethics

Ethical approval was not required.

5.4 Conflict of Interest

The authors declare that there are no conflicts of interest associated with this publication.

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6. Bibliography

[1] J. Mikulska, G. Juszczyk, M. Gawrońska-Grzywacz, and M. Herbet, "Hpa axis in the pathomechanism of depression and schizophrenia: New therapeutic strategies based on its participation," *Brain Sci.*, vol. 11, no. 10, 2021, doi: 10.3390/brainsci11101298.

[2] L. Cui *et al.*, *Major depressive disorder: hypothesis, mechanism, prevention and treatment*, vol. 9, no. 1. Springer US, 2024. doi: 10.1038/s41392-024-01738-y.

[3] D. G. Matthews *et al.*, "Centella asiatica improves memory and promotes antioxidative signaling in 5XFAD mice," *Antioxidants*, vol. 8, no. 12, 2019, doi: 10.3390/antiox8120630.

[4] G. Sbrini, P. Brivio, M. Fumagalli, F. Giavarini, D. Caruso, and …, "Centella asiatica L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex," *Nutrients*, 2020, [Online]. Available: https://www.mdpi.com/2072-6643/12/2/355

[5] A. N. Edinoff *et al.*, "Selective serotonin reuptake inhibitors and adverse effects: A narrative review," *Neurol. Int.*, vol. 13, no. 3, pp. 387–401, 2021, doi: 10.3390/neurolint13030038.

[6] M. Georg Jensen, M. Goode, and M. Heinrich, "Herbal medicines and botanicals for managing insomnia, stress, anxiety, and depression: A critical review of the emerging evidence focusing on the Middle East and Africa," *PharmaNutrition*, vol. 29, no. July, pp. 0–1, 2024, doi: 10.1016/j.phanu.2024.100399.

[7] P. Puttarak *et al.*, "Effects of Centella asiatica (L.) Urb. on cognitive function and mood related outcomes: A Systematic Review and Meta-analysis," *Sci. Rep.*, vol. 7, no. 1, pp. 1–12, 2017, doi: 10.1038/s41598-017-09823-9.

[8] Q. Ren *et al.*, "Asiaticoside improves depressive-like behavior in mice with chronic unpredictable mild stress through modulation of the gut microbiota.," *Front. Pharmacol.*, vol. 15, p. 1461873, 2024, doi: 10.3389/fphar.2024.1461873.

Doi: 10.30872/jtpc.v10i1.372

[9] L. Wang, T. Guo, Y. Guo, and Y. Xu, "Asiaticoside produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice, involving reversion of inflammation …," *Mol. Med.* …, vol. 22, no. 3, pp. 2364–2372, 2020, doi: 10.3892/mmr.2020.11305.

[10] A. Zhou *et al.*, "Asiaticoside Attenuates Chronic Restraint Stress-Induced Hippocampal CA1 Neuronal Ferroptosis via Activating BDNF/Nrf2/GPX4 Signaling Pathway.," *Drug Des. Devel. Ther.*, vol. 19, pp. 793–810, 2025, doi: 10.2147/DDDT.S509208.

[11] A. G. Bertollo *et al.*, "Hydroalcoholic Extract of Centella asiatica and Madecassic Acid Reverse Depressive-Like Behaviors, Inflammation and Oxidative Stress in Adult Rats Submitted to Stress in Early Life," *Mol. Neurobiol.*, vol. 61, no. 12, pp. 10182–10197, 2024, doi: 10.1007/s12035-024-04198-1.

[12] S. Jagadeesan *et al.*, "Prevention of Neuronal Damage in Brains of Chronic Stress-induced Male Wistar Rats Administering Centella asiatica (L) Urban," *J. Anat. Soc. India*, vol. 73, no. 3, pp. 204–213, 2024, doi: 10.4103/jasi.jasi_80_24.

[13] M. Ar Rochmah, I. M. Harini, D. E. Septyaningtrias, D. C. R. Sari, and R. Susilowati, "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 Res. Int.*, vol. 2019, 2019, doi: 10.1155/2019/264928[14] D. C. R. Sari, N. Arfian, U. Tranggono, and …, "Centella asiatica (Gotu kola) ethanol extract up-regulates hippocampal brain-derived neurotrophic factor (BDNF), tyrosine kinase B (TrkB) and extracellular …," *Iran. J.* …, 2019, [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC6885393/

[15] P. Chanana and A. Kumar, "Possible Involvement of Nitric Oxide Modulatory Mechanisms in the Neuroprotective Effect of Centella asiatica Against Sleep Deprivation Induced Anxiety Like Behaviour, Oxidative Damage and Neuroinflammation," *Phyther. Res.*, vol. 30, no. 4, pp. 671–680, 2016, doi: 10.1002/ptr.5582.

[16] A. Padmiswari, N. T. Wulansari, and K. B. Harditya, "EFEK NEUROPROTEKTIF EKSTRAK DAUN PEGAGAN (Centella asiatica) TERHADAP JUMLAH SEL NEURON HIPPOCAMPUS PADA MENCIT JANTAN (Mus …," *Ber. Biol.*, 2025, [Online]. Available: https://ejournal.brin.go.id/berita_biologi/article/view/13391

[17] E. Poleszak *et al.*, "Asiatic acid potentiates the activity of common antidepressant drugs in mice.," *Psychopharmacology (Berl).*, vol. 242, no. 12, pp. 2725–2737, Dec. 2025, doi: 10.1007/s00213-025-06827-6.

[18] L. Wang, T. Guo, Y. Guo, and Y. Xu, "Asiaticoside produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice, involving reversion of inflammation and the PKA/pCREB/BDNF signaling pathway," *Mol. Med. Rep.*, vol. 22, no. 3, pp. 2364–2372, 2020, doi: 10.3892/mmr.2020.11305.

[19] J. Jiang, R. Han, H. Ren, Y. Yao, and W. Jiang, "A review of neuroprotective properties of Centella asiatica (L.) Urb. and its therapeutic effects.," *Ann. Med.*, vol. 57, no. 1, p. 2559122, Dec. 2025, doi: 10.1080/07853890.2025.2559122.

[20] G. Wang *et al.*, "Corticosterone Impairs Hippocampal Neurogenesis and Behaviors through p21-Mediated ROS Accumulation," *Biomolecules*, vol. 14, no. 3, 2024, doi: 10.3390/biom14030268.

[21] S. Manohar *et al.*, "Unexpected Consequences of Noise-Induced Hearing Loss: Impaired Hippocampal Neurogenesis, Memory, and Stress," *Front. Integr. Neurosci.*, vol. 16, no. May, pp. 1–17, 2022, doi: 10.3389/fnint.2022.871223.

[22] T. F. A. França, "Isolating the key factors defining the magnitude of hippocampal neurogenesis' effects on anxiety, memory and pattern separation," *Neurobiol. Learn. Mem.*, vol. 166, 2019, doi: 10.1016/j.nlm.2019.107102.

[23] S. Liang *et al.*, "Administration of Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress," *Neuroscience*, vol. 310, pp. 561–577, 2015, doi: 10.1016/j.neuroscience.2015.09.033.

Doi: 10.30872/jtpc.v10i1.372

[24] Y. Wang *et al.*, "Hemerocallis citrina Baroni leaf total phenol alleviates depressive-like behaviors via modulating 'microbiota-gut-brain' axis in chronic unpredictable mild stress -induced rats," *Front. Pharmacol.*, vol. 16, no. September, pp. 1–17, 2025, doi: 10.3389/fphar.2025.1642515.
[25] Y. Chen, C. T. Ho, and X. Zhang, "The regulatory mechanism of intermittent fasting and probiotics on cognitive function by the microbiota-gut-brain axis," *J. Food Sci.*, vol. 90, no. 3, pp. 1–15, 2025, doi: 10.1111/1750-3841.70132.