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Review Article

Centella asiatica effect on traumatic brain injury: A systematic review

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ABSTRACT

Background: Mortality and morbidity in traumatic brain injury (TBI) cases remain a global problem. Various therapeutic modalities have been researched, including using herbal medicine. *Centella asiatica* has a lot of potential in neuropharmacology for various diseases. This systematic review aims to comprehensively review the currently available data about the impact of *C. asiatica* on TBI in a rat model.

Methods: Systematic searches were conducted on PubMed, Scopus, and Google Scholar up to July 2023. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Researchers screened the titles and abstracts of all identified studies and then selected relevant studies through full-text reviews. Studies reported the effect of *C. asiatica* on animal model of TBI were included in the study. Data were extracted, and the result was reported using descriptive analysis. The risk of bias was evaluated using SYRCLE.

Results: Four studies met the inclusion criteria. One study highlighted the potential neuroprotective effects of Asiatic acid, one study explored spade leaf extract phytosome, while the rest used *C. asiatica* extracts. The primary findings of the included research revealed that *C. asiatica* might reduce oxidative stress, decrease neuronal apoptosis, have anti-inflammatory properties, alleviate neurological dysfunction, reduce cerebral edema, and boost cognitive performance in the TBI-induced rat's model.

Conclusion: This review suggests that *C. asiatica* had the potential to benefit the TBI-induced rat model in terms of decreasing morbidity. Nevertheless, more studies are needed to perform a meta-analysis and ascertain the effects of *C. asiatica* on TBI in animal models.

Keywords: Centella asiatica, Brain injury, Rats model

INTRODUCTION

Traumatic brain injury (TBI) remains a significant global health issue, characterized by high rates of mortality and morbidity worldwide. Annually, the incidence of TBI is estimated to reach

50 million cases.[40] The leading causes of TBI are falls and traffic accidents.[11,37]

The pathophysiology of TBI involves various mechanisms resulting in brain injury, which can be categorized into primary and secondary injuries. Primary injury occurs immediately following a direct force impact, while secondary injuries develop subsequent to the initial impact.[4,32,37] In secondary brain injury, damage occurs to brain cells and tissues involving complex biochemical processes.[37]

No complete and effective treatment modalities currently exist for secondary injuries in TBI, which involve complex pathophysiology. Over the past few decades, extensive research has been conducted into various therapeutic approaches for TBI. Among these, the use of herbs as a complementary therapy has garnered significant attention.

Centella asiatica is a tropical also known as Asiatic pennywort, Indian pennywort, wild violet, tiger herb, Indian water navelwort, gotu kola, and pegagan, which is a vine herb that is widely used and cultivated as a medicinal plant in Asia.[17,20,38] *C. asiatica* contains numerous active constituents, the most significant of which are pentacyclic triterpenes, including Asiatic acid (AA), asiaticoside, madecassoside, and madecassic acid.[2,26]

C. asiatica has extensive pharmacological potential. Recent studies report *C. asiatica* to have roles in several conditions, such as reducing oxidative stress, antipyretic, antidepressant, anticonvulsant, anxiolytic, anticancer, anti-infective, anti-wrinkle, wound-healing, anti-inflammatory properties, and neuroprotective.[3,8,10,38]

Despite its wide use in various cases, the benefits of neuropharmacological use of *C. asiatica* in TBI are still receiving less attention. The clinical impact of *C. asiatica* on TBI has been researched through a number of randomized controlled trials. However, no studies summarize the evidence on the effects of *C. asiatica* on TBI and its associated potency. This study will thoroughly analyze all available data to verify the impact of *C. asiatica* on TBI and its related potency.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were used to conduct this systematic review. In addition, this systematic review follows the population, intervention, comparison, and outcome specification.

Search strategy

Several electronic databases were used in an electronic search for original publications from the beginning until July 2023, including PubMed, Science Direct, and Google Scholar. Literature search utilized keywords and filters in the form of Medical Subject Headings and text terms. The filters used were "*Centella*" AND "Brain Injury, Traumatic." Boolean operators (OR/AND) were used to combine words during the process, as shown in Table 1. In addition, relevant articles' references were scrutinized to identify any further studies of interest. Searches were conducted, and one researcher collected data from the selected articles, which another researcher examined.

Study selection

Studies that primarily discuss the effect of *C. asiatica* on TBI are included under the inclusion criteria. The review considers various study types, including experimental research such as clinical trials and randomized controlled trials using animal models, and included studies must prominently feature *C. asiatica* extract as the primary intervention and report relevant outcomes.

Conversely, exclusion criteria are equally crucial. Studies unrelated to the effects of *C. asiatica* on TBI will be excluded. Not in English, articles, reviews, letters, abstracts, or editorial papers will also be omitted.

Data extraction

A typical data extraction form was used for the data extraction process. Data extracted from each selected study included the main author, publication year, follow-up period, control group, and outcome in TBI.

Quality assessment

The systematic review authors used the SYRCLE's risk of bias tool to assess the quality of the included animal studies.[19] It was modified to account for characteristics of bias unique to animal intervention studies and is based on the Cochrane risk-of-bias tool. The tool evaluates six domains: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The tool also provides signaling questions to facilitate judgment and enhance transparency and applicability.

RESULTS

Out of 1128 identified articles, 68 were excluded due to duplication. After the duplicated articles were excluded, 1060 articles were screened. Only four studies met the inclusion criteria and were included in this study after 16 full-text articles were read, as shown in Figure 1. The studies included can be seen in Table 2.

Only four articles out of the more than a thousand initially found publications passed the requirements for inclusion in this systematic review [Table 3]. These studies investigated the effects of *C. asiatica* and its compounds on animal models

Table 1: Search strategies.

Patient/population	Intervention	Outcome	Study designs	Combining search terms
Animal model of brain injury	Administration of *Centella asiatica*	Effects of *Centella asiatica* on Traumatic Brain Injury	Clinical Trial OR Randomized Controlled Trial OR Controlled clinical trial	"*Centella asiatica*" AND "Brain Injury, Traumatic"

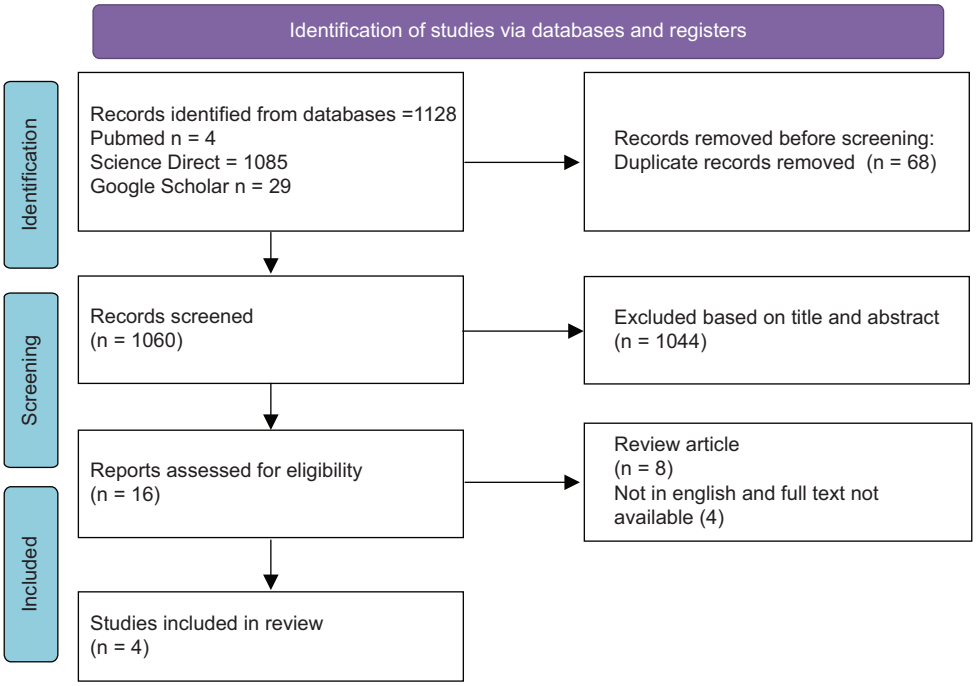

Figure 1: Flow diagram of the search strategy for *Centella asiatica* effect on traumatic brain injury.

of TBI. One study highlighted the potential neuroprotective effects of AA, a constituent found in *C. asiatica*, while another explored the effects of Spade Leaf Extract Phytosome (SEP), containing *C. asiatica,* and found improvements in nerve cells and cognitive function. Two studies investigated the impact of *C. asiatica* extracts; one investigated the immunoexpression of Bcl-2 and apoptosis in pyramidal cells, Krox-20, neuregulin I (NRG-I) expression, phospholipid distribution, and the other investigated the expression of tumor necrosis factor-alpha (TNF-α). The main findings of the included studies were attenuation of oxidative stress, decreased neuronal apoptosis, anti-inflammation, improvements in neurological dysfunction, decreased cerebral edema, and enhanced cognitive function in the TBI-induced rat's model.

The study conducted by Han *et al.*[18] administered AA at 30 mg/kg at 2 h and 6 h after rat-induced TBI. AA administration significantly reduced neurological severity scores compared with the TBI group ($P < 0.05$). The study results showed that the TBI group with AA administration significantly decreased brain water content compared to the TBI group without AA administration ($P < 0.05$). AA administration increased the expression of defense markers against oxidative stress (Nrf2 and HO-1) and reduced oxidative stress biomarkers' levels (Malondialdehyde [MDA], 4-Hydroxynonenal [4-HNE], and 8-hydroxydeoxyguanosine [8-OHdG]). AA administration has also been reported to reduce apoptosis. The study conducted by Jazmi *et al.* used the SEP model.[21] The study reported significant nerve cell improvement by activating several markers, including Krox-20, NRG-1 expression, and phospholipid distribution ($P < 0.05$). SEP administration also positively affected cognitive enhancement in the rat's model.

Nafiisah *et al.*[31] intervened in the TBI rats model by giving injections of extracts with doses of 150, 300, and 600 mg/kg body weight (BW)/day. The study evaluated apoptosis and immunoexpression of Bcl-2 from pyramidal cells. According to the study, *C. asiatica* extract can increase Bcl-2 immunoexpression in pyramidal cells and reduce apoptosis in the TBI-induced rat model. It was reported that 600 mg/kg BW of *C. asiatica* extract was the optimal dose in increasing Bcl-2 immunoexpression of pyramidal cells and suppressing apoptosis in the TBI rat model.

In a rat model of TBI, *C. asiatica's* impact on serum tumor

Table 2: Characteristics of studies that met the inclusion criteria.

Author, year	*C. asiatica* dose	Follow-up duration	Control	Expression	Outcome results
Han *et al*.,[18] 2018	Asiatic acid 30 mg//kg at 2 h and 6 h after TBI	Not specified	Sham group, TBI group without AA provision	Nrf2 and HO-1 expression; MDA, 4-HNE, and 8-OHdG	Nrf2 and HO-1 expression levels were upregulated and decreased the concentrations of 8-OHdG, 4-HNE, and MDA. Reduced brain edema and neuronal apoptosis, and it alleviated neurological functioning.
Jazmi *et al*.,[21] 2017	SEP 90 mg/kg BW	Not specified	No brain trauma, TBI without *C. asiatica* extract provision, and TBI with citicoline 25g/kg BW	Activation of Krox-20, NRG-1 expression	Nerve cell improvement via Krox-20 activation, NRG-1 expression, and increased phospholipid distribution. Enhancement of cognitive function.
Nafiisah *et al*.,[31] 2021	*C. asiatica* extract at 150, 300, and 600 mg/kg BW/d doses	7 days	No brain trauma and TBI without *C. asiatica* extract provision	Apoptosis, Bcl-2 of pyramidal cells	Decreased apoptosis and increased Bcl-2 immunoexpression of pyramidal cells in TBI
Nafiisah *et al*.,[30] 2021	*C. asiatica* extract at 150, 300, and 600 mg/kg BW/d doses	7 days	No brain trauma and TBI without *C. asiatica* extract provision	TNF-α levels	Reduced serum TNF-α levels in a TBI rat model.

C. asiatica: *Centella asiatica*, SEP: Spade leaf extract phytosome, TNF-α: Tumor necrosis factor-alpha, MDA: Malondialdehyde, 8-OHdG: 8-hydroxydeoxyguanosine, 4-HNE: 4-Hydroxynonenal, AA: Asiatic acid, TBI: Traumatic brain injury, BW: Body weight, NRG-I: Neuregulin I, Nrf-2 : nuclear related factor 2, HO-1: Heme oxygenase-1

Table 3: Risk of bias summary for the included studies on *Centella asiatica*.

	Han *et al*.[18] (2018)	Jazmi *et al*.[21] (2017)	Nafiisah *et al*.[31] (2021)	Nafiisah *et al*.[30] (2021)
Selection bias	Unclear	Unclear	Unclear	Unclear
Performance bias	No	Unclear	Unclear	Unclear
Detection bias	Unclear	Unclear	Unclear	Unclear
Attrition bias	Unclear	Unclear	Unclear	Unclear
Reporting bias	Unclear	Unclear	Unclear	Unclear

necrosis factor- levels were examined in a study by Nafiisah *et al*.[30] *C. asiatica* extract was utilized at doses of 150, 300, and 600 mg/kg BW/day. This study showed a significant decrease in TNF-α in TBI-induced rats given *C. asiatica* extract (P = 0,005).

Assessment of risk of bias of included studies

The SYRCLE's risk of bias tool is a checklist that evaluates the methodological quality of animal studies.[19] According to the systematic review's authors, most of the included studies had low quality overall and a high risk of bias. The studies also lacked transparency in reporting, making it difficult to assess the risk of bias accurately. The authors noted that SYRCLE's risk of bias tool helped evaluate the quality of the included animal studies and can facilitate and improve critical appraisal of evidence from animal studies. Therefore, the systematic review concluded that the included animal studies had a high bias risk and low evidence quality. The authors recommended that future animal studies adhere to the SYRCLE's risk of bias tool to improve the quality of evidence and reduce the risk of bias.

DISCUSSION

Research summarizing the role of *C. asiatica* in TBI has not been conducted to our knowledge. The study included four articles that fulfilled the eligibility criteria that had been set. In this study, we did not conduct a meta-analysis due to the limited data required. All four studies involved were preclinical studies using TBI-induced rat models that evaluated *C. asiatica* as a treatment modality for TBI.

The processes that occur in TBI include primary and secondary injuries. Damage and distortion to brain structures due to mechanical processes at the onset of trauma is known as

primary brain injury.[12] This process begins with damage to the blood–brain barrier (BBB) and failure of autoregulation in the brain.[24] This ultimately leads to increased intracranial pressure cerebral edema and ultimately reduces cerebral blood flow.[24]

After the initial trauma, secondary brain injury can happen hours, days, or even months later[15] and involve a variety of biochemical changes at the cellular and tissue level: (1) disturbance of homeostatic ion balance, (2) oxidative stress, (3) lipid degradation, (4) neurotransmitter release, (5) neuronal cell apoptosis, (6) inflammation response, (7) mitochondrial dysfunction, and (8) axon degeneration.[14,32,33,36]

Herbal plant research is currently prevalent throughout the globe. *C. asiatica* is one of the many botanical plants utilized in research. *C. asiatica* belongs to the family *Umbelliferae*.[23] Its major compounds are pentacyclic triterpenoids, phenols, saponins, sesquiterpene, eugenol derivatives, caffeoylquinic acids, and flavonoids.[16] The various constituents have been reported to have benefits for various diseases.

Cellular damage in secondary brain injury is primarily due to oxidative stress processes that produce reactive oxygen species.[13] The study by Han *et al*. reported the role of *C. asiatica* as antioxidative stress in TBI-induced rats.[18] AA, a constituent in *C. asiatica*, is reported to increase the expression of Nrf2 and HO-1 as markers of defense against oxidative stress. Other results reported were a decrease in oxidative stress parameters such as MDA, 4-HNE, and 8-OHdG. Administration of *C. asiatica* has the effect of increasing enzymes that are antioxidant.[41] Activation of this enzyme involves the Nrf2/ARE signaling cascade as an antioxidant response gene.[29]

C. asiatica also plays a role in the protection against neuronal cell apoptosis. In secondary brain injury, neuronal cell apoptosis occurs due to the activation of enzymes involved in cell apoptosis, such as caspases and calpain, by various biochemical signals.[32] Han *et al*. used TUNEL staining to assess the level of cell apoptosis.[18] This study reported decreased apoptotic cells in the group with AA intervention. This result was also confirmed by Nafiisah *et al*.[30] reported decreased cell apoptosis and increased expression of Bcl-2 as an antiapoptotic protein. Based on the literature, asiaticosides, a subclass of terpenoids, have antiapoptotic properties due to their ability to modulate the expression of Bcl-2 and Bax.[6,22] Various intracellular molecules are regulated by Bcl-2 in the mitochondrial membrane, including the release of cytochrome C, another protein that plays a role in cell apoptosis. Hence, ultimately, increased Bcl-2 expression can inhibit cell apoptosis.[35]

The role of *C. asiatica* as an anti-inflammatory was reported by the study of Nafisah *et al*.,[30] which evaluated TNF-α levels in TBI-induced rats. BBB dysfunction that occurs in TBI within the first 24 hours leads to activation of the inflammatory response.[27] There is infiltration of neutrophils, monocytes, lymphocytes, and inflammatory mediators such as interleukin (IL)-1b, IL-6, and TNF-α.[27,32] The mechanism of programmed cell death can occur through caspase activation by TNF-α through interaction with Fas ligands.[1] Triterpenes of *C. asiatica*, specifically AA, asiaticoside, and madecassoside were reported in preclinical studies in stroke to have anti-inflammatory effects by reducing microglia activation cytokine levels.[7,25,28] Results from recent studies show similar results that *C. asiatica* extract can suppress nuclear factor-kappa B, which acts as a transcription factor in inflammation, and reduce other proinflammatory cytokines, including TNF-α.[34]

TBI causes a decrease in phospholipids, and this condition can last for an extended period. Phospholipids are membrane constituents and play a role in re-myelination.[39] Phospholipid depletion is a risk for future neurodegenerative diseases such as Parkinson's and Alzheimer's.[39] The study of Jazmi *et al*.[21] demonstrated that SEP increased the activation of Krox-20, the expression of NRG-1, the enhancement of neurological functions, and the distribution of phospholipids following the induction of the TBI model in rats. Krox-20 is a gene that controls the myelination process through the Schwann cell ErB2 receptor and activates NRG-1 signaling.[5] Furthermore, Jazmi *et al*.[21] also explored the combination of *C. asiatica* extract and citicholin. The results reported improved cognitive function compared to *C. asiatica* extract or citicoline alone. In addition, Han *et al*. investigated neurological dysfunction and brain edema. Han *et al*.[18] reported that AA effectively reduced brain tissue's water content, thereby enhancing the permeability of the compromised BBB and protecting brain tissue.[9]

Limitations of the review

The systematic review of the effect of *C. asiatica* on TBI has several limitations that should be considered when interpreting the findings. First, the review included only four studies that met the inclusion criteria, which may not provide a comprehensive overview of the effects of *C. asiatica* on TBI. Second, the included studies varied in terms of study design, sample size, duration of intervention, and outcome measures, which may limit the ability to draw definitive conclusions about the effects of *C. asiatica* on TBI. Third, the included studies have a high risk of bias, which may affect the validity of the review's findings. Fourth, the included studies used different dosages and formulations of *C. asiatica,* which may affect the consistency of the results. Fifth, the studies involved are limited to animal models; human studies are needed for high-quality studies. Finally, the review was conducted primarily in English, which may have resulted in language bias. Relevant studies published in other languages may have been missed, which may affect the comprehensiveness of the review.

CONCLUSION

While the systematic review provides evidence suggesting that *C. asiatica* may have a positive effect on TBI, the study's limitations should be considered when interpreting the findings. Additional high-quality research is necessary to confirm the effects of *C. asiatica* on TBI and determine the optimal dosage and formulation of *C. asiatica* for treating TBI.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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