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HERBAL MEDICINE AS AN ADJUVANT THERAPY IN EXPERIMENTAL TRAUMATIC BRAIN INJURY: A SCOPING REVIEW OF TYPES, DOSAGES, AND TREATMENT DURATION IN RAT MODELS

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ABSTRACT
Traumatic brain injury (TBI) is associated with substantial neurological morbidity and mortality, and current therapeutic approaches remain limited in targeting secondary injury mechanisms. This scoping review aimed to summarize the types, dosages, treatment durations, and therapeutic effects of herbal medicine as an adjuvant therapy in experimental TBI models. A literature search was conducted in PubMed, ScienceDirect, Scopus, Springer Link, and additional sources using predefined eligibility criteria focused on rodent TBI models and herbal interventions. Thirteen studies published between 2016 and 2025 were included. Most studies were preclinical experiments using male rats or mice, while two clinical randomized controlled trials involving TBI patients were also identified. The reviewed interventions included Centella asiatica, luteolin, Pycnogenol, rhubarb, rhein, cinnamon extract, Yunnan Baiyao, TH-CD, Xuefu Zhuyu Decoction, and herbal combinations. Treatment duration typically ranged from 3 to 14 days. Overall, herbal interventions demonstrated potential neuroprotective effects by reducing neuroinflammation, oxidative stress, neuronal apoptosis, edema, and disruption of the blood–brain barrier, leading to improvements in neurological, histopathological, and selected clinical outcomes.

Keywords: adjuvant therapy; blood–brain barrier; herbal medicine; neuroinflammation; neuroprotection; rodent model; traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) is a condition characterized by changes in brain function or evidence of other brain pathology caused by an external force. Research estimates that approximately half of the world's population will experience at least one episode of TBI in their lifetime (Maas et al., 2017). Studies in developed countries indicate that TBI is the leading cause of death and disability among young adults (Majdan et al., 2016). The annual incidence worldwide ranges from 100 to 300 cases per 100,000 people, but the actual number of TBI cases— —is much higher. In high-income countries, falls are the most common cause of trauma. When broken down by age, traffic accidents are common among young adults, while falls are more common among children and the elderly (Brazinova et al., 2021).

An evaluation of TBI cases from several healthcare facilities in Indonesia revealed varying prevalence and mortality rates. A study at Prof. Dr. Margono Soekarjo Hospital in 2021–2022 identified 624 TBI cases, with a mortality rate of 7.69% (Nabila et al., 2024). Another study at West Nusa Tenggara Hospital from 2015 to 2017 identified 209 cases of TBI, of which 33 patients (15.79%) died, 2 patients (0.96%) were in a vegetative state, and 18 patients (8.61%) experienced severe disabilities (Rosyidi et al., 2019). A study at Bina Sehat Hospital in Jember from 2023 to 2025 identified 356 cases of TBI, of which 11.5% of patients died (Widiyawati et al., 2025). Although various therapeutic approaches have been implemented in the management of TBI, the high rates of disability and mortality reported indicate that the effectiveness of existing therapies is not optimal in improving short- and long-term clinical outcomes. Most current therapies focus on hemodynamic stabilization and the prevention of secondary injury, but do not specifically target complex pathophysiological mechanisms such as neuroglial inflammation, oxidative stress, and progressive neuronal death (Rosyidi et al., 2019; Widiyawati et al., 2025).

The clinical outcome of TBI patients varies widely depending on the impact of contusions, diffuse cellular damage, intracranial hematoma, and axonal injury. TBI occurs not only in the acute phase but often becomes a chronic process, with progressive injury occurring over several years (Maas et al., 2015). Primary and secondary brain injury are classifications of the damage processes that occur in brain injuries. In TBI, primary brain injury occurs during the initial trauma and is caused by the displacement or deformation of the brain's physical structures. Secondary brain injury develops gradually and involves various cellular processes (Ortega-Pérez & Amaya-Rey, 2018). Secondary injuries, which are not caused directly by mechanical damage, can occur as a consequence of the primary injury or independently. These conditions include ischemia (decreased blood flow), cerebral hypoxia (lack of oxygen to the brain), hypotension (low blood pressure), cerebral edema (swelling of the brain), changes in cerebral blood flow, and increased intracranial pressure, which is the pressure inside the skull (Ng & Lee, 2019a).

Several animal studies have explored various adjuvant therapies to improve patient clinical outcomes, but the findings have yielded mixed results. A study administering oral Centella asiatica (L.) extract demonstrated a significant reduction in serum TNF-α levels, decreased apoptosis, and increased Bcl-2 immunoexpression in a mouse TBI model (Nafiisah, Prihatno, et al., 2021a; Nafiisah, Faniyah, et al., 2021a). Another study that administered intraperitoneal Pycnogenol (PYC) showed a significant reduction in lesion volume and protection of brain synaptic function but was unable to improve performance on the Morris Water Maze, a measure of cognitive function (Scheff & Roberts, 2016a). Research using oral cinnamon extract (CE) supplementation has shown that CE can mitigate visual and spatial memory impairments, as well as reduce neuronal loss in the temporal cortex and dentate gyrus. Research involving the intravenous administration of negatively charged carbon dots (CDs)—a combination of Semen pruni persicae and Carthamus tinctorius L. (TH-CDs) intravenously is able to reduce the permeability of the blood-brain barrier (BBB), improve the recovery of neurological function, reduce brain edema and neuronal damage, and increase the expression of claudin 5 and ZO-1 (Scheff & Roberts, 2016a).

This scoping review focuses on evaluating the effectiveness and safety of herbal remedies as adjuvant therapy for TBI. It comprehensively summarizes research findings related to herbal types, optimal dosages, and treatment durations tested in rodent models of experimental traumatic brain injury. This approach is highly relevant given that TBI is a complex neurological condition characterized by changes in brain function due to external forces, with a significant global incidence and high morbidity and mortality rates. (Arora et al., 2023; Moura et al., 2023). This study aims to evaluate the effectiveness and safety of various herbs as adjuvant therapy in traumatic brain injury (TBI) through a comprehensive review of experimental studies in rodent models, as well as to identify the types of herbs, optimal doses, and duration of administration that have the potential to provide therapeutic benefits in the treatment of TBI.

METHOD

Study Design

This study employed a scoping review design, a method aimed at comprehensively exploring a specific topic (Peterson et al., 2017). The process of conducting this scoping review followed a methodological framework based on Arksey and O'Malley (Arksey & O'Malley, 2005), further refined by Levac et al. (2010), which comprises five main stages: (1) formulating the research question, (2) identifying relevant studies, (3) selecting studies, (4) mapping data, and (5) synthesizing, summarizing, and reporting findings. Based on the established framework, this study formulated the main research question: What is the role of herbal medicine as an adjuvant therapy in traumatic brain injury?

Search Method

A literature search was conducted using the PubMed, ScienceDirect, Scopus, Wiley, and MEDLINE databases from December 1–15, 2025. A systematic, literature search strategy was developed to identify studies relevant to both research questions. Keywords were formulated and aligned with Medical Subject Headings (MeSH) and combined using the Boolean operators AND and OR to ensure comprehensive search coverage. The terms used included combinations of population, outcomes, and care context, namely: (("traumatic brain injury" OR "TBI" OR "brain trauma" OR "brain injury") AND ("herbal medicine" OR "alternative medicine" OR herbal OR plant OR curcuma) AND ("adjuvant therapy" OR protect OR neuroprotection OR recovery OR neuroregeneration OR neuroinflammation OR neuroplasticity OR therapy OR neuro)). This search strategy was designed to capture various forms, doses, and durations of herbal medicine administration in traumatic brain injury.

Eligibility Criteria

To ensure that the retrieved articles are relevant to the research question, the following framework was used:

Population (P) : Rats (rodent models) with traumatic brain injury (TBI).

Intervention (I) : Administration of herbal medicine as an adjuvant therapy (various types of herbs with varying doses and durations).

Comparison (C) : A group of TBI-injured mice that did not receive herbal medicine or that received a placebo or standard therapy.

Outcome (O) : Improvement in neurological and neurobiological outcomes, including reduced inflammation and apoptosis, protection of the blood–brain barrier, enhanced neuronal regeneration, and improved cognitive and motor function.

Inclusion criteria for this study include original research articles written in English, published between 2015 and 2025 to ensure the currency of the scientific evidence, and specifically evaluating the use of herbal medicine as an adjuvant therapy in mouse models of traumatic brain injury, with clear reporting on the type of herbs, dosage, and duration of administration. Secondary data-based studies, as well as books or book chapters, were excluded from the review.

Study Selection

The article selection process was conducted by four researchers (BY, YB, SB, MTA) based on the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Page et al., 2021). The selection process was conducted using Mendeley to ensure relevance to the research topic and to systematically identify the outcomes to be reported (Rožanc & Mernik, 2021). The screening stages included checking for duplicates, selection based on inclusion and exclusion criteria, and assessment of alignment with the established PCC framework. After the screening process was completed, all researchers reviewed the full text of each article to assess its suitability and relevance to answering the research questions. Any disagreements among researchers were resolved through discussion until a consensus was reached.

Quality Assessment

Quality assessment is not mandatory in a scoping review design (Xue et al., 2024). However, this step was still conducted by the researchers as a form of transparency in the review process (Peters et al., 2015). The quality assessment of the articles was performed by three researchers (BY, YB, SB) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist 2020. The assessment criteria are based on a percentage score, with >70% categorized as high quality, 50–70% as moderate quality, and <50% as low quality (Melo et al., 2018). We adapted the JBI criteria to align with bias risk assessment standards, namely the Cochrane Risk of Bias (RoB) and bias risk in non-randomized intervention studies. Each criterion was then assessed using the following options: "Yes," "No," "Unclear," or "Not Applicable." If a criterion was rated "Yes," it was assigned a score of 1. If rated "No" or "Unclear," it was assigned a score of 0. The scores for each criterion were then summed to obtain a total score for each study. Disagreements in the assessment were resolved through discussion with two experts (YB, MTA) and by involving all researchers until a consensus was reached. All articles in this study were categorized as having a low risk of bias.

Data Extraction and Synthesis

Before data synthesis was conducted, the researchers extracted study results using the "Update Guidance for Conducting Systematic Scoping Reviews" (Peters et al., 2020). Two researchers (BY, MTA) worked in pairs to extract information, including article details such as authors, year, study design, objectives, country of study, population, and study results (see Table 1). After data extraction was complete, the researchers synthesized the data to identify the type, dose, and duration of the herbal medicine used.

Three researchers (BY, YB, SB) synthesized the findings narratively using an inductive approach by reading, organizing, and developing categories (Elo & Kyngäs, 2008). The authors then engaged in in-depth discussions to synthesize the extracted data, identify key themes and patterns, and draft a brief summary for each article to capture key ideas. To enhance clarity and facilitate synthesis, interventions identified in the literature were carefully grouped based on similarities to form categories of similar interventions; each category was then described and elaborated upon to provide a comprehensive understanding of the range of interventions and their effects. All analysis steps were independently verified by all authors to ensure accuracy and consistency; disagreements were addressed through a review of relevant data and systematically discussed until consensus was reached, in order to guarantee the reliability of the findings and ensure that the review process was thorough, transparent, and met standards of scientific rigor.

RESULT

Study Selection

The study selection process was conducted according to the PRISMA 2020 guidelines. During the identification phase, articles were retrieved from four databases: PubMed (9 articles), ScienceDirect (24 articles), Scopus (58 articles), and Springer Link (701 articles). Additionally, studies were identified through other methods, including citation searching (3 articles) and manual searching (4 articles). Prior to the screening stage, 10 articles were excluded due to duplication, 19 articles were excluded because they were deemed ineligible through an automated process, and 6 articles were excluded for other reasons. During the screening phase, 859 articles were screened based on their titles and abstracts. Of these, 704 articles were excluded because their study designs did not meet the review criteria. Subsequently, 155 reports were sought for full-text access, but 132 reports could not be included because their study populations were inappropriate. Thus, 23 reports from the primary databases were assessed for eligibility during the eligibility phase.

During the eligibility phase, 23 reports were assessed based on inclusion and exclusion criteria. Of these, 8 reports were excluded because they were book chapters, 4 because their research findings were unclear, and 5 because they were review articles. Meanwhile, through the supplementary

search method, 7 reports were identified; all were successfully obtained and deemed eligible without exclusion. After the entire selection process was completed, 13 studies met the inclusion criteria and were included in this scoping review.

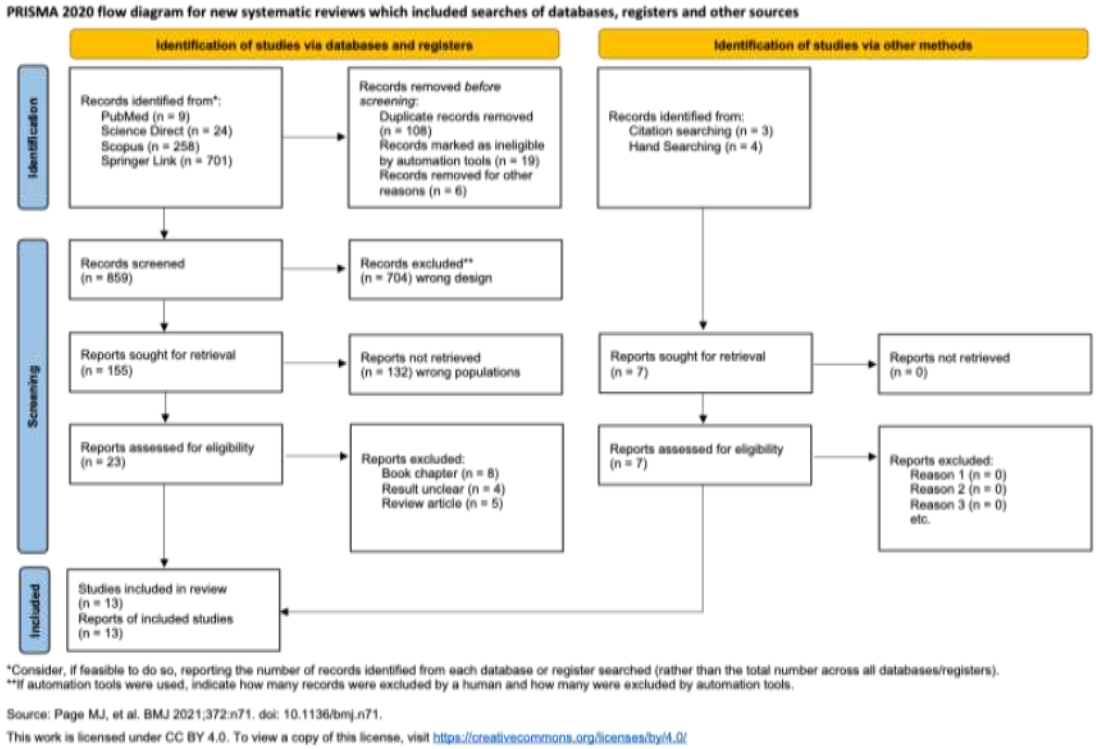

Figure 1. PRISMA Flowchart

Participant Characteristics

Most of the included studies used preclinical traumatic brain injury models involving male rats or mice, primarily the C57BL/6, Wistar, Sprague–Dawley, and ICR strains. The reported animal subjects were generally young adults, with ages ranging from 6 to 12 weeks or 2 to 3 months, and body weights between 150 and approximately 300 g. Only two studies involved human participants with traumatic brain injury. These included postoperative neurosurgical patients and 54 ICU patients who were assigned to intervention and control groups, while the remaining studies focused on animal-based or experimental laboratory models.

Study Characteristics

The included studies were published between 2016 and 2025 and were conducted across five countries: China, Indonesia, the United States, Israel, and Iran. China contributed the largest number of studies, followed by Indonesia and the United States. Most studies were preclinical experimental studies using traumatic brain injury models, while two studies were clinical randomized controlled trials involving patients with traumatic brain injury. The study designs varied across the included articles, including in vivo animal experiments, in vitro laboratory studies, molecular docking, network pharmacology, metagenomic analysis, and randomized controlled trials. The interventions evaluated were primarily herbal or plant-derived compounds, such as luteolin, Centella asiatica, Pycnogenol, Yunnan Baiyao, rhubarb, cinnamon extract, and Xuefu Zhuyu Decoction. The intervention duration ranged from 3 to 14 days in most studies, although one study administered treatment both before and after TBI induction.

Table 1.
Main Findings

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
1	Yu et al. (2024)	China	Experimental study using in silico (molecular docking) and in vivo methods with a controlled cortical impact (CCI) model.	Identified the primary therapeutic targets of medicinal plants that are potentially effective against traumatic brain injury (TBI) and evaluated the effects of luteolin in a TBI model.	Molecular docking: 16 articles related to herbal medicines for TBI. In vivo: 8-week-old male C57BL/6 mice, 5 mice per group: sham, TBI, TBI + AZD3759 15 mg/kg, TBI + luteolin 25 mg/kg, and TBI + luteolin 50 mg/kg.	Luteolin at 25 and 50 mg/kg was compared with the selective EGFR inhibitor AZD3759 at 15 mg/kg; administered intraperitoneally once daily.	14 days	Brain tissue histopathology (HE and Nissl), expression of GFAP, EGFR, brevican, DAPI, GAP43, mNSS score, and body weight changes on days 7 and 14.	Luteolin binds strongly to the active pocket of EGFR. Administration of luteolin or AZD3759 improved body weight recovery and neurological function, reduced astrocyte activation and EGFR expression, decreased chondroitin sulfate proteoglycan deposition, and increased GAP43 expression in the cortex.	12/13 Low risk
2	Nafiisah et al. (2021)	Indonesia	True experimental study with a post-test-only controlled group design.	Assessing the anti-inflammatory effects of Centella asiatica (L.) extract through a reduction in serum TNF-α levels in a mouse model of TBI.	35 male Wistar rats (Rattus norvegicus), divided into 5 groups: P1 (normal); P2 (TBI + CMC); P3 (TBI + Centella asiatica extract 150 mg/kg body weight/day); P4 (TBI + 300 mg/kg body weight/day); P5 (TBI + 600 mg/kg body weight/day).	Centella asiatica extract doses of 150, 300, and 600 mg/kg body weight/day. Specific administration methods were not reported.	7 days	Serum TNF-α levels.	TNF-α levels differed significantly among groups (Kruskal–Wallis, p = 0.005). Mean TNF-α levels: P1 = 60.980 ± 4.057; P2 = 76.931 ± 0.698; P3 = 75.889 ± 0.948; P4 = 75.868 ± 1.163; P5 = 74.508 ± 1.126. Centella asiatica extract has the potential to reduce serum TNF-α levels in a TBI model.	11/13 Low risk
3	Scheff et al. (2016)	United States	Experimental study in laboratory animals.	Assessing the post-traumatic therapeutic potential of Pycnogenol in reducing cognitive	38 male Sprague–Dawley rats, divided into the following groups:	Pycnogenol (PYC) 50 or 100 mg/kg; administered via intraperitoneal injection at 15 minutes, 3	7 days	Cognitive function (Morris Water Maze), lesion volume, and	High-dose Pycnogenol significantly reduced cortical lesion volume but did not improve	12/13 Low risk

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
				dysfunction and protecting neurons following TBI.	sham + saline vehicle, TBI + saline vehicle, TBI + low-dose Pycnogenol, and TBI + high-dose Pycnogenol.	hours, and 6 hours post-injury.		Fluoro-Jade B staining.	Morris Water Maze performance compared to the control group. Pycnogenol also did not reduce the number of Fluoro-Jade B-positive neurons in the hippocampus.	
4	Nafiisah et al. (2021)	Indonesia	True experimental study with a post-test-only controlled group design using a mouse model of TBI.	Evaluated the effects of Centella asiatica (L.) extract on apoptosis and Bcl-2 immunoexpression in pyramidal cells in a mouse model of TBI.	Male Wistar rats aged 2–3 months weighing 150–200 g, with 7 rats in each group: P1 (normal); P2 (TBI); P3 (TBI + 150 mg/kg body weight/day); P4 (TBI + 300 mg/kg body weight/day); P5 (TBI + 600 mg/kg body weight/day).	Centella asiatica extract at 150, 300, and 600 mg/kg body weight/day, administered orally.	7 days	Pyramidal cell apoptosis and Bcl-2 immunoreactivity.	Centella asiatica extract significantly increased Bcl-2 expression and reduced neuronal apoptosis in a dose-dependent manner. A dose of 600 mg/kg body weight exhibited the strongest neuroprotective effect .	13/13 Low risk
5	Chen et al. (2021)	China	Randomized controlled trial (RCT).	To evaluate the efficacy of Yunnan Baiyao as an adjunctive therapy in patients with TBI following neurosurgery, particularly regarding neurological recovery, inflammation, oxidative stress, coagulation, and clinical outcomes.	Patients with TBI following neurosurgery. The control group received conventional postoperative therapy; the intervention group received conventional therapy + Xingnaojing 20 mL/day, low-dose Yunnan Baiyao 1 g/day, or	Yunnan Baiyao was administered orally, while Xingnaojing was administered intravenously.	14 days post-surgery	Glasgow Coma Scale (GCS), serum S100B levels, serum superoxide dismutase (SOD) levels, and clinical prognosis based on the Glasgow Outcome Scale (GOS) and the Karnofsky Performance Scale.	The adjunctive therapy group showed a faster and higher improvement in GCS scores ($p < 0.01$), a faster decrease in S100B levels, better recovery of SOD activity, and better 3-month clinical outcomes compared to the control group. Xingnaojing and Yunnan Baiyao have the potential	13/13 Low risk

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
					high-dose Yunnan Baiyao 2 g/day.				to improve recovery and prognosis through improvements in the S100B and SOD biomarkers.	
6	Luo et al. (2022)	China	In vivo and in vitro laboratory experimental studies.	Evaluated the neuroprotective effects of TH-CD on blood-brain barrier (BBB) permeability and neurological recovery following a CCI-modeled TBI.	Male C57BL/6 mice, 8–10 per group: sham, TBI, and TBI + TH-CD via tail vein injection.	TH-CD 100 μL/day, derived from Semen pruni persicae (Taoren) and Carthamus tinctorius L. (Honghua) using a hydrothermal method without organic solvents; administered via intravenous tail vein injection.	3 days	mNSS on days 0, 1, and 3; brain water content; HE, Nissl, and immunohistochemical histopathology; BBB function assessed via Evans Blue and IgG ; molecular docking; and safety testing on cells, peripheral blood, and organs.	TH-CD is biocompatible and repairs BBB damage, as demonstrated by a reduction in Evans Blue and IgG extravasation , as well as increased expression of claudin-5 and ZO-1. TH-CD also reduces neuroinflammation, brain edema, and neuronal degeneration, and enhances post-TBI functional recovery.	12/13 Low risk
7	Zheng et al. (2025)	China	A laboratory experimental study combining network pharmacology, metagenomics, and in vivo validation.	Evaluated the therapeutic mechanisms of rhubarb in TBI by integrating direct pharmacological targets and gut microbiota-mediated effects.	Adult male C57BL/6 mice aged 6–8 weeks, 10 mice per group: sham, TBI, TBI + low-dose rhubarb (0.6 g/kg), medium-dose (1.2 g/kg), and high-dose (2.4 g/kg).	Rhubarb granules at doses of 0.6, 1.2, and 2.4 g/kg were administered orally.	3 days	Neurobehavioral function (mNSS and wire hang test), HE and Nissl histopathology, neuronal apoptosis via TUNEL and IgG, BBB permeability, and expression of GFAP, TNF-α, and IL-1β.	Rhubarb exerts neuroprotective effects by inhibiting neuronal apoptosis and inflammation, maintaining BBB integrity, and modulating gut microbiota and short-chain fatty acid (SCFA) metabolism. These effects are thought to occur through multi-target mechanisms and interactions within the microbiome–brain axis.	13/13 Low risk
8	Qubty et al.	Israel	In vivo experim	Assessed the effects	Male ICR strain rats	aqueous cinnamon	was adm	Memory, motor	Cinnamon extract	12/13 Low

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
	(2020)		ental study.	of aqueous cinnamon extract consumption on cognitive function and neuronal condition following TBI.	were divided into 4 groups: control, cinnamon extract- d without TBI, TBI without cinnamon extract, and TBI + cinnamon extract.	extract (CE) was administered orally via drinking water at a concentration of 100 µg/mL.	istered 1 week before TBI and continued for 2 weeks after TBI	activity, anxiety, and neuronal survival.	significantly prevented post-TBI visual and spatial memory impairments ($p < 0.01$–0.001). Immunohistochemical results showed a reduction in neuronal loss in the temporal cortex and dentate gyrus of the hippocampus compared to the untreated TBI group ($p < 0.05$–0.01).	risk
9	Norris et al. (2016)	United States	Experimental animal study using the controlled cortical impact (CCI) model.	Assessed the effects of Pycnogenol on CA3–CA1 hippocampal synaptic function following TBI.	Male Sprague–Dawley rats were divided into the following groups: 7-day saline vehicle (n = 8), 7-day Pycnogenol (n = 9), 14-day saline vehicle (n = 7), and 14-day Pycnogenol (n = 8).	Pycnogenol 10 mg/kg was administered via a single intravenous injection 15 minutes after injury.	7 and 14 days	Basal synaptic strength, long-term depression (LTD), and CA3–CA1 synaptic function.	TBI reduced the amplitude of the field excitatory postsynaptic potential (fEPSP) in the CA3–CA1 pathway of the hippocampus. Pycnogenol significantly restored the fEPSP amplitude to near-normal levels ($p < 0.05$) and reduced neuronal damage and tissue edema in the hippocampal region.	12/13 Low risk
10	Wang et al. (2016)	China	In vivo experimental study in Sprague–Dawley rats using a CCI model and in vitro study using a	To assess whether rhubarb and its active component, rhein, protect the BBB after TBI by inhibiting the gp91phox/ NADPH oxidase–ROS–	In vivo: 8–10-week-old male Sprague–Dawley rats, weighing 200–250 g, n = 6–8 per group: control, TBI, TBI + rhubarb 3/6/12 g/kg, TBI +	Rhubarb, rhein, and apocynin. In the in vivo model, they were administered orally; in the in vitro model, they were administered as cellular treatments.	Not reported	Brain water content, Evans Blue extravasation, ZO-1 and MMP-9 expression in brain tissue, and RT-PCR for ZO-1, MMP-9,	Rhein was detected in the brain following rhubarb administration. Rhubarb and rhein significantly reduced BBB permeability and brain edema, suppressed the	13/13 Low risk

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
			scratch-wound model in primary rat cortical astrocytes.	ERK–MMP-9 pathway, and to compare the neuroprotective effects of rhein with those of rhubarb.	rhein 12 g/kg, and TBI + apocynin 50 mg/kg. In vitro: primary cortical astrocytes with control, scratch injury, scratch + rhubarb 200 μg/mL, scratch + rhein 20 μM, and scratch + apocynin 100 μM groups.			β-actin, gp91phox, p-ERK, and ERK.	expression of gp91phox, ROS, p-ERK1/2, and MMP-9, and increased ZO-1 expression both in vivo and in vitro. The BBB-protective effects of rhein were equivalent to those of rhubarb and similar to those of apocynin.	
11	Rosyidi et al. (2024)	Indonesia	An experimental study using Sprague–Dawley rats with a TBI model induced by the Marmarou method.	To determine the neuroprotective effects of a combination of Centella asiatica, cinnamon, and spirulina on acute TBI based on histopathological findings.	Male Sprague–Dawley strain rats (Rattus norvegicus), 10–12 weeks old, weighing ±300 g, n = 15 per group: control (TBI + placebo) and treatment (TBI + Centella asiatica + cinnamon + spirulina).	Oral administration of the combination of Centella asiatica, cinnamon, and spirulina.	7 days	GFAP expression as a histopathological marker of brain injury.	There was a very strong correlation between administration of the herbal combination and increased GFAP expression ($r = 0.818$; $p = 0.004$). The treatment group showed increased GFAP expression in astrocytes as well as less tissue damage— , and necrosis— compared to the control group.	10/13 Low risk
12	Malekahmadi et al. (2021)	Iran	Double-blind randomized controlled trial (RCT).	To assess the effects of French maritime pine bark extract supplementation on inflammatory, clinical, and nutritional status in TBI patients	54 TBI patients in the ICU, consisting of 29 patients in the intervention group and 25 patients in the control group.	French maritime pine bark extract (Oligopin)—3 capsules per day, each containing 50 mg—was administered alongside enteral nutrition; the control group received a	10 days	IL-6, IL-1β, CRP, total antioxidant capacity (TAC), malondialdehyde (MDA), APACHE II, SOFA, NUTRIC score, and survival rate.	The intervention reduced IL-6 ($\beta = -53.43$ pg/mL; $p = 0.006$), IL-1β ($\beta = -111.66$ pg/mL; $p = 0.002$), CRP ($\beta = -19.99$ mg/L; $p < 0.001$), APACHE II ($\beta = -3.72$; $p = 0.001$),	9/13 Low risk

No.	Author (Year)	Country	Design/ Method	Objective	Population/ Sample	Intervention and Administration Method	Duration	Outcome Variables	Primary Outcome	Risk of Bias
				treated in the ICU.		placebo.			SOFA (β = −2.07; p < 0.001), and NUTRIC score (β = −0.60; p = 0.01). The survival rate was reported to be 15% higher than in the control group.	
13	Yang et al. (2025)	China	Experimental study in rats with TBI induced by controlled cortical impact (CCI).	Evaluated the neuroprotective effects of Xuefu Zhuyu Decoction (XFZYD) on BBB function following TBI.	Male Sprague–Dawley rats, 6–7 weeks old, weighing 240 ± 10 g, n = 10 per group: sham, CCI, and CCI + XFZYD 9 g/kg administered orally for 3 days.	Xuefu Zhuyu Decoction (XFZYD) 9 g/kg administered orally.	3 days	BBB integrity based on the expression of collagen IV, occludin, ZO-1, MMP-9, COX-2, β-actin, as well as metabolite markers such as adenosine, creatinine, linoleic acid, 8,11,14-eicosatrienoic acid, oleic acid, palmitoleic acid, 4-oxoproline, L-phenylalanine, and L-norleucine.	XFZYD repairs post-TBI blood-brain barrier (BBB) damage by increasing tight junction and basement membrane proteins (occludin, ZO-1, collagen IV), suppressing MMP-9 and COX-2, and regulating adenosine metabolism through a reduction in ENT2.	10/13 Low risk

Type of intervention

Herbal medicines identified in experimental studies of traumatic brain injury include single-plant extracts, plant-derived active compounds, herbal combinations, herbal-based nanomaterials, and traditional herbal formulations. Interventions used include *Centella asiatica*, luteolin, Pycnogenol, rhubarb, rhein, cinnamon extract, TH-CD, a combination of *Centella asiatica*, cinnamon, and spirulina, and Xuefu Zhuyu Decoction. Study findings indicate that these herbal interventions play a role in various mechanisms of secondary injury following TBI, particularly inflammation, blood-brain barrier damage, neuronal apoptosis, cerebral edema, histopathological abnormalities, and impaired neurological and cognitive function.

Dosage

Dosages used in experimental TBI studies vary depending on the type of intervention, dosage form, route of administration, and outcomes assessed. *Centella asiatica* was used in a range of low to high

doses and was associated with changes in inflammatory markers and neuronal apoptosis, while luteolin demonstrated effects on neurological function and astrocyte activation. Rhubarb and rhein are used in relatively higher doses because they are in the form of extracts or herbal granules, while Pycnogenol shows varying results ranging from a reduction in lesions to improvements in synaptic function and cognitive function. These findings indicate that the biological response to dosage is not always consistent across all outcome parameters.

Duration

The administration of herbal medicine in experimental TBI models generally occurs during the acute to subacute phases following injury. Shorter treatment durations are used to assess early changes such as cerebral edema, inflammation, and blood-brain barrier disruption, while longer durations are used to assess neuronal apoptosis, histopathological changes, protein expression, recovery of neurological function, cognitive function, and tissue regeneration. Most studies administered the intervention after TBI induction; therefore, the findings obtained better illustrate the use of herbal medicine as a post-injury adjuvant therapy.

DISCUSSION

In *traumatic brain injury* (TBI), there are two types of related injuries that significantly influence patients' clinical outcomes: primary injury, in which neural tissue undergoes mechanical damage, leading to hemorrhage, contusion, impaired cerebral blood flow (CBF), disruption of the blood-brain barrier (BBB), and metabolic abnormalities (Ng & Lee, 2019b). These processes continue for a long time after the initial injury, ranging from several days to months, or even years. Ultimately, neuroinflammation and neurodegeneration lead to neurological deficits (Hanscom et al., 2021). Secondary injury often involves multiple processes, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axonal degeneration, and apoptosis (Buccilli et al., 2024). Oxidative stress mediated by superoxide radicals and various *reactive oxygen species* (ROS) is thought to be a major factor triggering inflammation and impaired neural function (Kim et al., 2019). The acute inflammatory response in TBI differs between the early and late phases. Prolonged excessive inflammation can hinder the recovery process. Following a brain injury, the body produces large amounts of pro-inflammatory cytokines, including IL-1β, IL-6, and CRP (Vaughan et al., 2018).

In cases of TBI, IL-1β is the most abundantly produced cytokine. Glial cells produce IL-1β, which then affects neurons and other brain cells. IL-1β plays a role in stimulating the inflammatory response, recruiting immune cells, disrupting *the blood-brain barrier* (BBB), causing edema, and leading to neuronal loss (Muballe et al., 2019). Elevated levels of IL-1β are detected in cerebrospinal fluid and brain tissue within a few hours after brain injury. Administration of anti-IL-1β antibodies has been shown to reduce edema and brain tissue damage (Clausen et al., 2011).

Similar findings have also been observed with IL-6. Interventions that reduce IL-6 levels in animals with mild TBI are able to restore brain function to near-normal levels and reduce the effects of hypoxia, which exacerbates inflammatory brain damage. In TBI patients, CRP levels are associated with the length of stay in the intensive care unit (ICU), dependence on a ventilator, and the severity of the injury (Naghibi, 2017). Various herbal ingredients are used as part of intervention strategies to improve clinical outcomes in TBI patients by preventing secondary injury through the suppression of the inflammatory response (Wang et al., 2016; Yu et al., 2024). The herbal ingredients used include *Centella asiatica* extract, *French maritime pine bark extract* (Pycnogenol and Oligopin), cinnamon extract, luteolin, and Yunnan Baiyao, which contains the active compound Panax notoginseng saponins (PNS), a combination of Semen pruni persicae and Carthamus tinctorius L., rhubarb, rhein, Spirulina, and Xuefu Zhuyu Decoction (Wang et al., 2025). These various herbal agents were selected based on their pharmacological potential, such as anti-inflammatory, antioxidant, anticoagulant, and neuroprotective effects, which are expected to

contribute to the improvement of the clinical condition of the study subjects (L. Chen et al., 2021; Malekahmadi et al., 2021a; Nafiisah, Prihatno, et al., 2021b; Nafiisah, Faniyah, et al., 2021b; Norris et al., 2016; Qubty et al., 2021a; Rosyidi et al., 2024; Scheff & Roberts, 2016b).

Centella asiatica is known to possess a wide range of pharmacological activities, such as neuroprotective, nerve regenerative, immunomodulatory, antidepressant, memory-enhancing, gastroprotective, cardioprotective, radioprotective, anticancer, antimicrobial, wound-healing, anti-inflammatory, antidiabetic, and antioxidant properties. *Centella asiatica* contains a diverse complex of chemical compounds, with the main groups including terpenes (monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes), phenolic compounds (flavonoids, tannins), alkaloids, carbohydrates, vitamins, minerals, and amino acids. Triterpenoids, one of the major compound groups in *Centella asiatica*, consist of madecassoside, asiaticoside, madecassic acid, and asiatic acid (Sabaragamuwa et al., 2018).

Asiaticoside is one of the most well-known triterpenoids and has been the subject of intensive research due to its potential to enhance collagen synthesis and wound healing, as well as its potent anti-inflammatory effects (He et al., 2023). Asiaticoside stimulates collagen synthesis by upregulating transforming growth factor beta 1 (TGF-β1) and fibronectin, promotes the formation of new blood vessels (angiogenesis), and contributes significantly to tissue regeneration. These effects make asiaticoside highly beneficial in treating various skin conditions, including wounds, burns, and scars. Furthermore, recent studies have demonstrated the role of asiaticoside in promoting neurogenesis through upregulation of BDNF, suggesting potential for the treatment of neurodegenerative diseases (Zhou et al., 2025).

Madecassoside is a glycoside—specifically a triterpene saponin—with a structure very similar to asiatic acid (Mandal et al., 2023). Madecassoside also plays a key role in inhibiting the activation of nuclear factor kappa B (NF-κB), reducing cytokine-induced inflammation, protecting against UV-induced skin aging, and aiding in wound healing. Madecassoside is also known for its anti-inflammatory properties and its ability to boost collagen production, which is crucial for skin repair. Recent studies show that nanoparticles containing madecassoside have improved transdermal delivery and stability in dermatological applications (Lu et al., 2023).

Asiatic acid ($C_{30}H_{48}O_5$) and madecassic acid ($C_{30}H_{48}O_6$) are pentacyclic triterpenoids. These compounds exhibit anti-inflammatory, anticancer, hepatoprotective, and neuroprotective properties through the modulation of the *mitogen-activated protein kinase* (MAPK), *nuclear factor erythroid 2-related factor 2* (Nrf2), and *phosphatidylinositol 3-kinase/protein kinase B* (PI3K/Akt) signaling pathways (Tan et al., 2021). Madecassoside also exhibits anti-inflammatory and antioxidant effects, which may contribute to its overall wound-healing properties (Kraft et al., 2022).

Another potent antioxidant with anti-inflammatory effects, as demonstrated by various studies, is *French maritime pine bark extract*. This compound consists of several oligomers, including the flavan-3-ol catechins, epicatechin, taxifolin, caffeic acid, and ferulic acid. Based on pharmacological studies, the mechanism of action of this herbal medicine involves a reduction in NF-κB activity in monocytes, followed by the inhibition of matrix metalloproteinases. The clinical effects of this herbal extract include endothelium-dependent vasodilation and antithrombotic effects, which have been demonstrated through various in vitro studies, in vivo animal studies, and clinical trials in humans (Tan et al., 2021).

French maritime pine bark extract also exhibits inhibitory effects on the enzymes cyclooxygenase-1 and cyclooxygenase-2. These factors play a role in the inflammatory process and the elevation of pro-inflammatory markers. Inhibition of these pathways leads to a reduction in levels of CRP, IL-1β, and IL-6. This indicates an immunomodulatory effect, a reduction in inflammation, and an

improvement in patients' clinical condition following administration of *French maritime pine bark* extract (Malekahmadi et al., 2021b). French *maritime pine bark extract* is also capable of preventing neurotoxicity and apoptotic cell death under conditions of oxidative stress. This herbal medicine provides protection against lipid peroxidation, pro-oxidants, and peroxynitrite (Hadi et al., 2019). Several animal studies have demonstrated the protective effects *of French maritime pine bark extract* following traumatic brain injury through the suppression of IL-6 and TNF-α levels (Scheff et al., 2013).

Cinnamon is known to reduce oxidative stress and various neuronal inflammatory processes through its active component, sodium benzoate—a cinnamon metabolite and food additive—which plays a role in reducing the inflammatory response of microglia and astrocytes (Qubty et al., 2021b). Trans-cinnamaldehyde, an active component of cinnamon, has been shown to inhibit cytotoxic edema and reduce the expression of *inducible nitric oxide synthase* and *cyclooxygenase-2* in a cerebral ischemia model (Y.-F. Chen et al., 2016). Cinnamon also reduces brain MDA levels and increases the activity of antioxidant enzymes such as SOD, CAT, and GSH-Px. These effects demonstrate cinnamon's potential to reduce oxidative damage and inflammation in TBI through the regulation of the antioxidant transcription factor Nrf2 (Bai et al., 2017).

Cinnamon's anti-inflammatory mechanism is associated with reduced NF-κB activation, followed by decreased expression of the pro-inflammatory cytokines IL-1 and IL-6. The phenolic compounds in cinnamon are also known to enhance the neuroprotective activity of Sirtuin-1 (Sirt1) and suppress the expression of the pro-inflammatory protein NF-κB (Zhang et al., 2016). The interaction between Sirt1, NF-κB, and Nrf2 plays a crucial role in regulating oxidative and chronic inflammatory responses (Brennemen et al., 2017; Yoon et al., 2016). These findings suggest that cinnamon has the potential to serve as a therapeutic agent for reducing inflammation and oxidative stress in TBI through the modulation of the Sirt1-mediated NF-κB/Nrf2 signaling pathway (de Mingo et al., 2016).

Cinnamon administration has also been shown to reduce the expression of GFAP and IL-6, which is associated with the modulation of astrocyte responses via the IL-6/JAK/STAT pathway. Suppression of the inflammatory cascade is known to enhance axonal regeneration following TBI. Cinnamon administration can significantly increase the expression of NCAM, a molecule involved in remyelination, new neuron regeneration, and synaptic remodeling. The increase in NCAM indicates that cinnamon's anti-inflammatory properties can create an environment that supports neuroregeneration following TBI (Yulug et al., 2018).

Luteolin is a natural polyphenolic flavonoid found in various plants. This compound possesses a wide range of biological activities, including anti-inflammatory, antioxidant, anticancer, antimicrobial, anti-ulcer, antiviral (against influenza), cytoprotective, hepatoprotective, neuroprotective, neurotrophic, neurogenic, cardioprotective, modulation of macrophage polarization, and free radical scavenging activities. Dietary sources of luteolin include olive oil, oranges, celery, parsley, carrots, lemons, scallions, green tea, apple peel, thyme, oregano, peppermint, green bell peppers, broccoli, rosemary, perilla, fenugreek seeds, and chamomile flowers. Luteolin is able to cross *the blood-brain barrier* (BBB) by modulating Rho GTPase, thereby exerting neuroprotective effects (Kempuraj et al., 2021a).

Mast cells act as effector cells, sensors, and initiators of the immune response, initiating, amplifying, and sustaining both immune and neuronal responses following activation. Mast cells are found in the brain parenchyma and meninges, particularly around cerebral blood vessels, and function to regulate BBB permeability during immune responses and neuroinflammation. Following brain injury, neurotrauma, or stroke, mast cells are among the fastest to respond to maintain homeostasis through the release of anti-inflammatory and neuroprotective cytokines and

chemokines. Optimal mast cell activation provides neuroprotective effects. Excessive activation, however, leads to the stimulation of astrocytes, microglia, and neurons through the release of inflammatory mediators that exacerbate neuroinflammation, neuronal death, and cognitive decline. Mast cells can also activate glial cells via direct CD40-CD40L interactions . The activated glial cells then produce additional inflammatory mediators that, in turn, reactivate mast cells and other glial cells, thereby forming a continuous inflammatory cycle. Under these conditions, luteolin plays a crucial role by inhibiting the activation of mast cells, glial cells, and neurons. This effect helps suppress neuroinflammation and neurodegeneration (Kempuraj et al., 2021b).

Panax notoginseng [(Burk.) F.H. Chen], also known as Sanqi, is a Chinese herbal plant widely used for the treatment of stroke and cerebrovascular disorders. This plant possesses various hematological and pharmacological effects, including regulation of platelet aggregation, reduction of blood viscosity, improvement of blood circulation, cerebral vasodilation, analgesic, antihyperlipidemic, hemostatic, anti-edema, antihyperglycemic, antioxidant, anti-inflammatory, and anti-apoptotic effects. *Panax notoginseng* saponin extract (PNS) is known to improve learning and memory impairments in animals by inhibiting oxidative stress and apoptosis and stimulating neurogenesis. The main constituents of PNS include ginsenosides Rg1, Rb1, and notoginsenoside R1, which are present in high concentrations along with more than 20 other types of ginsenosides (Xu et al., 2015).

PNS and some of its active components exhibit protective effects against ischemia-reperfusion injury in the brain, heart, and kidneys. Ginsenoside Rb1 prevents endothelial dysfunction by activating the PI3K/Akt pathway and inhibiting PKC. Ginsenoside Rg1 enhances post-hypoxic angiogenesis via the HIF-1α, GR, and VEGFR pathways, while notoginsenoside Ft1 stimulates blood vessel formation by regulating the PI3K/AKT and Raf/MEK/ERK pathways. PNS also enhances VEGF signaling, inhibits apoptosis, and supports the proliferation and differentiation of neural stem cells, thereby contributing to the recovery of neurological function following intracerebral hemorrhage (ICH). Several studies have shown that ginsenosides Rb1, Rd, and Rg1 can enhance neurogenesis, peripheral nerve regeneration, and learning and memory functions (Xu et al., 2015).

In addition to its neuroregenerative effects, PNS exhibits potent antioxidant and anti-inflammatory activity. PNS increases the expression of thioredoxin-1 and prevents neurotoxicity caused by oxidative stress. Ginsenoside Rb1 acts as a free radical scavenger, inhibits apoptosis, protects neurons from beta-amyloid toxicity, and activates the ERK1/2/Akt pathway. Ginsenoside Rd exhibits neuroprotective effects in experimental stroke by reducing redox imbalance, inhibiting inflammation, decreasing iNOS and COX-2 expression through NF-κB suppression, and enhancing glutamate clearance. Ginsenoside Rg1 also inhibits NF-κB activation, reduces oxidative stress, and suppresses the inflammatory response in various disease models. Overall, PNS has the potential to serve as a neuroprotective therapeutic agent through its antioxidant, anti-inflammatory, anti-apoptotic, and angiogenic activities, as well as its stimulation of neurogenesis (Xu et al., 2015).

Preliminary research on the pharmacological mechanisms of carbon dots derived from Chinese herbal medicine (*Chinese herbal medicine-derived* CDs/CHM-CDs) has revealed various potential therapeutic activities. The hemostatic effects of CHM-CDs are thought to be related to the regulation of both endogenous and exogenous coagulation pathways. CHM-CDs are also capable of regulating various signaling pathways and cytokines, thereby providing a protective effect on organ tissues. Furthermore, CHM-CDs can inhibit neurotoxicity caused by nerve excitation and increase levels of serotonin (5-HT) and norepinephrine (NE), thereby contributing to neuroprotective and analgesic effects (Zhao et al., 2025).

CHM-CDs also exhibit anti-inflammatory activity through the regulation of inflammatory cytokine levels. The immunomodulatory effects are evident through the inhibition of M1 macrophage polarization and a relative increase in M2 macrophage polarization, which is associated with tissue repair and inflammatory resolution. These mechanisms demonstrate the potential of CHM-CDs to control the inflammatory response and maintain immune system balance (Zhao et al., 2025). CDs synthesized hydrothermally from *Semen Pruni Persicae* and *Carthamus tinctorius* L. have been shown to improve the recovery of neurological function following traumatic brain injury in mice. Administration of these compounds reduces blood-brain barrier (BBB) permeability, decreases brain edema, and suppresses neuronal damage. These protective effects were also accompanied by increased expression of claudin-5 and ZO-1 in brain tissue, which play a crucial role in maintaining BBB integrity (Zhao et al., 2025).

CONCLUSION

Herbal medicine shows promising potential as an adjunctive therapy for traumatic brain injury by attenuating key mechanisms of secondary brain injury, including neuroinflammation, oxidative stress, neuronal apoptosis, cerebral edema, and blood-brain barrier disruption, with corresponding improvements in neurological and histopathological outcomes. However, considerable heterogeneity in herbal formulations, dosages, treatment protocols, and study designs limits direct comparison and clinical translation.

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