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# The effect of *Centella asiatica*, cinnamon, and spirulina as neuroprotective based on histopathological findings in ratus Sprague Dawley with traumatic brain injury

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## ABSTRACT

**Background:** Traumatic brain injury (TBI) is a global health problem with the potential to cause dangerous neurological problems. Based on histopathological findings in Sprague Dawley (SD) rats with TBI in the acute phase, the study seeks to discover the effect of *Centella asiatica*, cinnamon, and spirulina as neuroprotective.

**Methods:** We conducted an experimental study with 30 SD rats randomly divided into three groups. The intervention was the administration of *C. asiatica*, cinnamon, and spirulina to the control and the experimental groups. Histological features were assessed using hematoxylin and eosin (H&E) staining and immunohistochemical examination. The data were analyzed using statistical analysis through correlation tests.

**Results:** The test samples' average body weights had $P > 0.05$, indicating no significant difference in the test sample body weights. Therefore, the variations in the expression level of the dependent variable were expected to be caused by the induction of brain injury and the administration of *C. asiatica*, cinnamon, and spirulina. In addition, the variables were not normally distributed. Thus, the Spearman test was carried out and showed the correlation was very strong, with a value of $r = 0.818$ and $P < 0.05$.

**Conclusion:** Based on histopathological findings from the brains of SD rats with TBI, pegagan, cinnamon, and spirulina will protect the brain (neuroprotective) in the acute phase.

**Keywords:** *Centella asiatica*, Cinnamon, Neuroprotective, Spirulina, Traumatic brain injury

## INTRODUCTION

Brain injury is still a significant health problem throughout the world due to an increasing incidence.[43] The most common causes of brain injury are 45% due to traffic accidents, 30% due to falls, 10% accidents during recreation, and 5% due to assaults. Brain injuries more often affect men than women, the age range between 15 and 34 years.[2,8,11,12]

Traumatic brain injury (TBI) is a condition that occurs when the structure of the head is impacted and causes disruption of brain function.[5,49] This condition is one type of injury that has the most common contribution to disability and mortality.[3,43] In addition, TBI could cause dangerous effects on neurological function in self-regulation and social behavior and increase the risk of behavioral disorders.[4,7,41,46,47]

According to Basic Health Research in 2018, the prevalence of brain injury in Indonesia is around 11.9%. Injuries to the brain occupy the third most common injury after injuries to the lower limbs and upper limbs, with a respective prevalence of 67.9% and 32.7%. The province of West Nusa Tenggara is the fourth leading contributor to brain injury patients.[40]

Brain injuries may occur from rotational forces as the brain moves within the skull or can be caused directly by external forces acting on the brain. Before brain damage, persistent cognitive abnormalities were noted in 15–40% of persons.[36] The three distinct cognitive domains of complex attention (multitasking), executive function (planning and decision-making), and cognitive flexibility (rapid task switching) had the highest prevalence of long-term defects.[12-14]

In addition, patients may feel fatigue, anxiety, sadness, and neurobehavioral consequences (such as headaches, lightheadedness, and sensitivity to noise). These deficiencies can affect a person's daily functioning, frequently affecting their quality of life, social interactions, and capacity to return to work.[15,20] Damaged cells and nerve connections can be repaired and regenerated by the brain following a TBI. Nevertheless, oxidative stress, a disturbance in the equilibrium between the body's anti-oxidation defenses and the generation of harmful reactive oxygen species, or free radicals, followed an injury, which resulted in additional brain damage and slowed healing.[33,37,46] Reducing oxidative damage from reactive oxygen species and promoting healing can be achieved by enhancing the body's natural antioxidant supply.[18,23] Some studies show that antioxidant therapy stabilizes edema, improves cognitive function, neurobehavioral sequelae, and reduces mortality after TBI.[24,25,32]

*Centella asiatica* is a wild plant that is efficacious as a traditional medicine for various diseases. Since ancient times, *C. asiatica* has been used to treat skin problems (e.g., keloids) and nervous disorders and improve blood circulation.[26,27] A small 2016 study compared the effects of *C. asiatica* extract and folic acid in improving cognitive function after stroke. This study assessed its impact on three groups of participants; one took 1000 milligrams (mg) of *C. asiatica* daily, one took 750 mg of *C. asiatica* daily, and one took 3 mg of folic acid daily. In research, *C. asiatica* extract had a modest effect in protecting brain cells from toxicity.[29-31]

Cinnamon or *Cinnamomum zeylanicum* is a spice produced from the dry inner skin, which is very aromatic, sweet, and spicy. People used it in sweet baked foods and hot wine, which was also used as medicine.[2] Kalipada Pahan of Rush University Medical Center, in a journal published in 2015 in the National Library of Medicine, fed mice a mixture of cinnamon powder and water and then did several experiments.[28] Therefore, cinnamon may have anti-inflammatory effects on the brain and other central nervous systems. It also suggests that cinnamon may control immunological reactions.[2,18,21]

Spirulina is an herbal supplement that contains various vitamins, minerals, and antioxidants that are beneficial for body health.[9] Spirulina is often referred to as a superfood because it has complete nutrition and high protein content. Spirulina is believed to provide various benefits, such as improving the immune system.[9,38]

Assessing TBI is challenging, but blood glial fibrillary acidic protein (GFAP) can predict intracranial pathologies undetectable on head computed tomography scans.[1,19] It is commonly used for prognostic and follow-up in patients with negative imaging results. GFAP also evaluates nervous injury in induced head trauma in animal models, aiding brain injury research.[10,34,51]

This research aimed to examine the neuroprotective properties of *C. asiatica*, cinnamon, and spirulina in relation to acute TBI. We intend to determine how these natural compounds affect the degree of brain injury and the healing process, focusing on its histological findings. This study attempts to provide insights into new treatment strategies to address the worldwide health burden of TBI.

## MATERIALS AND METHODS

We conduct an experimental observational-analytic study by administering medication as an intervention and then analyzing outcomes. This research was done in the Laboratory of the Faculty of Medicine, University of Mataram. Research samples consist of white Wistar rats with the strain Sprague Dawley (SD), with the criteria of the male gender, 10–12 weeks of age, body weight 300 g, and in good health.

The independent variables in this study were treatment of TBI and *C. asiatica*, cinnamon, and spirulina. Meanwhile, the dependent variable is the histopathological picture of necrosis markers in the acute phase.

The tools used for hematoxylin and eosin (H&E) staining and Immunohistochemistry (IHC) examination in this study were a slide warmer, antigen retrieval declocking chamber, micropipette, microtome, object glass, cover glass, PAP PEN, tissue, light microscope, and tray.

The materials include paraffin blocks of mice biopsies that had been administered according to their group, xylol I, xylol II, and xylol III, absolute alcohol, 90%, 80%, and

70% alcohol, 0.5% hydrogen peroxide ($H_2O_2$), liliemayer's hematoxylin, and enthelan.

The sample consisted of mice SD, who met the criteria and were randomly divided into two treatment groups: the control group (given a placebo) and the treatment group (given a combination of *C. asiatica*, cinnamon, and spirulina). The sample was anesthetized with ketamine following craniotomy with a coronal incision. After the dura mater was exposed, the sample was dropped with a weight of 40 g from a height of 20 cm using a Marmarou model. The Marmarou model is a simple brain injury treatment technique.

Mice SD, 3–4 months old, weighing 300 g, were placed in groups (five animals per group) in cages with a room temperature of 25 ± 1°C. Lighting was set on a 12-h light and 12-h dark cycle (the light cycle starts from 6:00 a.m. to 6:00 p.m.). Food and beverages were available in sufficient quantities, acclimatized for 7 days, and eaten and drank *ad libitum*. Ill or dead experimental animals are excluded from the study. Their body weight was measured, and the mice were assigned to treatment groups randomly.

After all the above was done, the rat's brain SD will be taken using a micro craniotomy surgical technique and then made into a paraffin block. Paraffin blocks that have been sorted, can be identified, and are not damaged will proceed to the IHC examination stage and H&E staining.

HE samples and paraffin block of rat brain SD were then sent to the anatomy pathology analysis department in Surabaya. The examination began with cutting the H&E paraffin block of rat brain SD 4–6 microns thick, then placing it on a glass object. The immunohistochemistry (IHC) examination carried out is for the acute phase group in the form of GFAP. Then, the preparation was observed with a light microscope with a total magnification of 400 times to interpret the examination. Then, anatomical pathology specialists interpret the preparation. This study used primary data, which was then analyzed using the SPSS computer program.

## RESULTS

We did a statistical analysis to obtain an interpretation of the results concerning the conceptual framework and research hypotheses. This study found the mean of *Rattus norvegicus* strain SD body weight of 290.07 (+10.48) g using the Lavene homogeneity test presented in Table 1.

**Table 1:** Sprague Dawley rat body weight.

| | Rat body weight (g) | *P*-value |
|---|---|---|
| Average | 290.07 | 0.155 |
| SD | ±10.48 | |

Description: Body weight homogeneity test of Sprague Dawley rat as an injury model brain, SD: Standard deviation

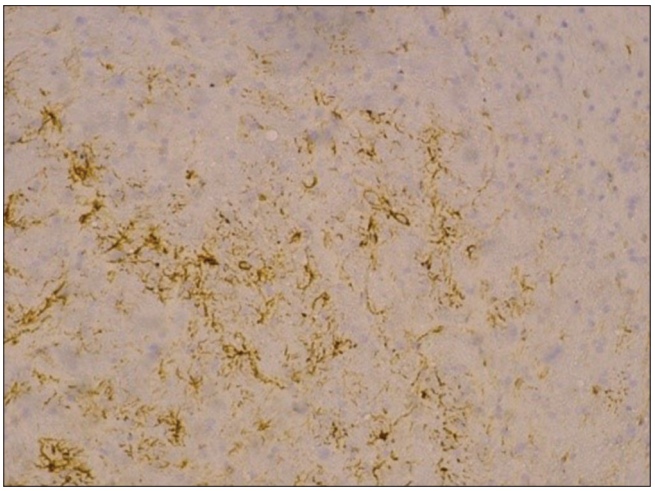

**Figure 1:** Immunohistochemistry, glial fibrillary acidic protein (GFAP), ×200 experimental group. This shows a positive GFAP antibody stain on the neural cell membrane.

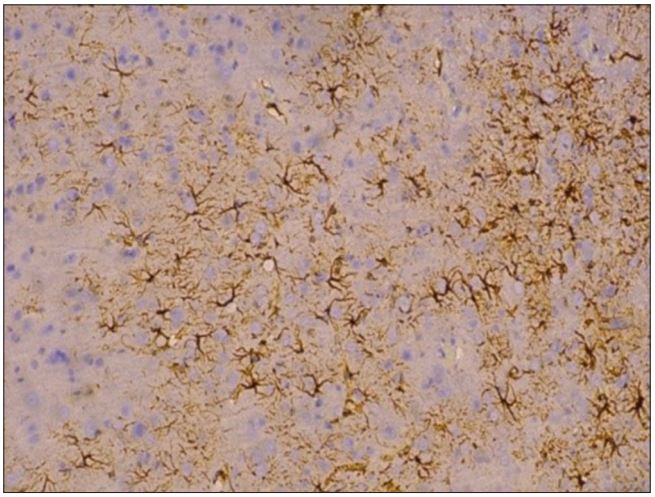

**Figure 2:** Immunohistochemistry, glial fibrillary acidic protein (GFAP), ×200 control group. This shows that GFAP is negatively stained on the neuronal cell membrane.

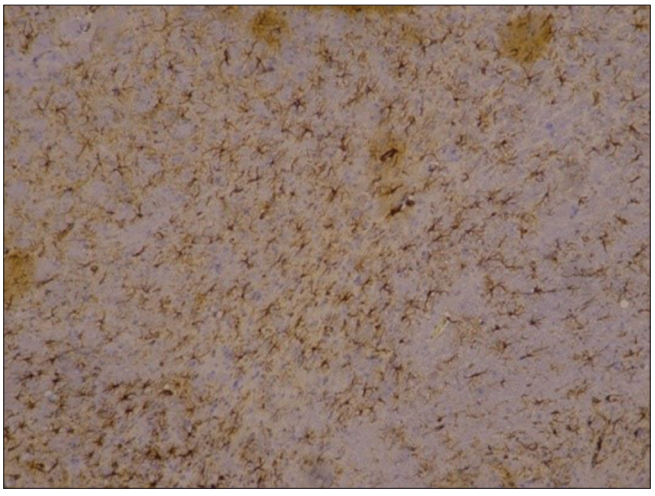

**Figure 3:** Glial fibrillary acidic protein normal rat.

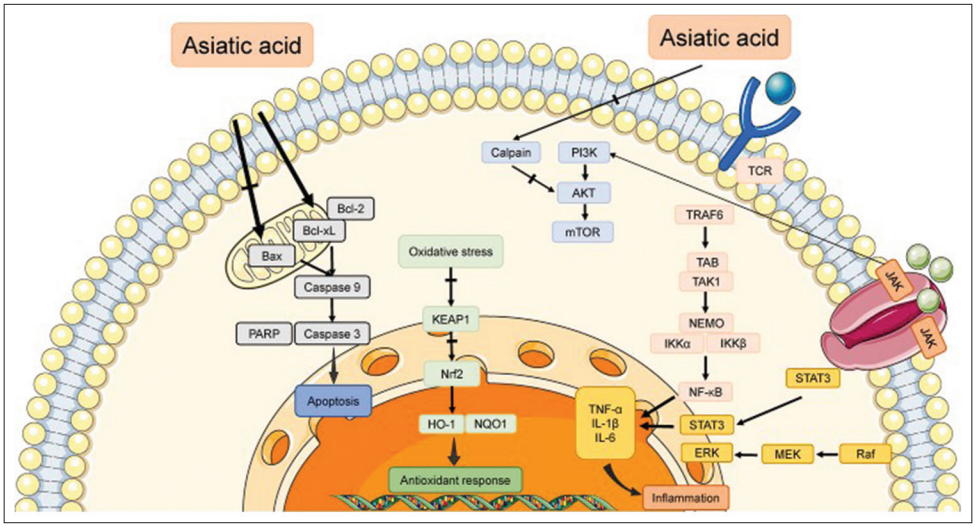


**Figure 4:** The neuroprotective mechanism of Asiatic acid. Nrf2: Nuclear Factor Erythroid 2-related Factor 2, Bcl-2: B-cell lymphoma 2, Bcl-xL: B-cell lymphoma-extra large , Bax: BCL2 Associated X, Apoptosis Regulator, PARP: Poly (ADP-ribose) polymerase, KEAP1: Kelch-like ECH-associated protein 1, NQO1: NAD(P)H dehydrogenase (quinone) 1, HO-1: heme oxygenase , AKT: protein kinase B, PI3K: phosphatidylinositol 3-kinase, mTOR: mechanistic Target of Rapamycin, TNF-α:Tumor necrosis factor alpha, IL-1β: interleukin 1-beta , IL-6: interleukin 6, TRAF6: Tumor necrosis factor receptor (TNFR)-associated factor 6 , TAK1Transforming growth factor beta-activated kinase 1, TAB: TAK1-binding proteins, NEMO: NF-κB Essential Modulator , IKKA: IκB kinase, NF-κB: Nuclear Factor kappa B , STAT3: signal transducer and activator of transcription 3, MEK: Mitogen-activated protein kinase/ERK kinase, JAK: Janus Kinase

**Table 2:** Correlation test results.

| | |
|---|---|
| Correlation coefficient | 0.818 |
| Significance | 0.004 |

Based on Table 1, $P > 0.05$, meaning the mice's body weight was not significantly different. Thus, it was anticipated that variations in the expression of different dependent variables would reflect the impact of brain damage induction and the administration of *C. asiatica*, cinnamon, and spirulina. Brain injury occurs when external forces cause damage to brain tissue, as opposed to degenerative or congenital processes, which may result in altered consciousness.

This study uses a brain injury model in Marmarou Modification.[30] By performing a histological analysis of the tissue, it was conceivable to demonstrate if the trauma could result in brain damage. The immunohistochemistry feature of GFAP for the experimental group can be seen in Figure 1, the control group in Figure 2, and the normal rat in Figure 3.

The association between GFAP during the acute phase and intervention provision was interpreted using a correlation test. In the control group, the intervention dose was considered to be 0; in the intervention group, the dose was 1. The normality test of GFAP for both groups used the Kolmogorov–Smirnov normality test. It was found that both tests were not normally distributed in the intervention group ($P < 0.005$, 0.003) and the placebo group ($P < 0.05$, 0.013). Thus, the Spearman test was carried out, and the results of the bivariate test with the Spearman correlation test are presented in Table 2.

Table 2 shows that statistically, there was a significant correlation, with $P > 0.005$ ($P = 0.004$). These results imply that the administration of C. asiatica, cinnamon, and spirulina may significantly impact GFAP levels during the acute stage of TBI. The observed rise in GFAP levels following intervention points to a possible neuroprotective role for the natural compounds in reducing inflammation and neuronal damage.

## DISCUSSION

Asiatic acid (AA), the most important component of asiaticoside, is present in *C. asiatica* extracts.[22] Asiaticoside is an aglycone form of pentacyclic triterpenoid found naturally in plants. It possesses many biological functions, including anti-inflammatory, antioxidant, anti-infective, and anti-tumor properties.[27] AA has also been the subject of extensive research in recent decades. Numerous neurological conditions, including spinal cord injury, cerebral ischemia, epilepsy, TBI, neural tumors, Alzheimer's disease, and Parkinson's disease, have demonstrated significant promise

for therapy with it.[48] Furthermore, AA offers relevant information on neuroprotective signaling pathways, and its significant neuroprotective potential makes it a unique contender for developing innovative central nervous system-targeting medications. By lowering the amount of pro-apoptotic Bax protein and raising the concentration of anti-apoptotic Bcl-xL protein, AA prevents neuronal mitochondrial death. The neuroprotective mechanism of Centella asiatica can be seen in Figure 4.[13]

One of the main causes of disability and mortality, particularly in young adults, is TBI.[4] Moreover, oxidative stress plays a crucial role in the initiation and progression of TBI. Plant-based substances can help TBI patients with neurological abnormalities, reduce brain edema and neuronal death, and combat oxidative stress.[27] In a study using an SD rat TBI model,[17] observed that the treatment of AA alleviated neurological impairments, reduced neuronal death, and reduced TBI-induced brain edema *in vivo*. Furthermore, it has been discovered that AA can decrease the increased concentrations of several substances, including malondialdehyde, 4-hydroxy-2-nonenal, and 8-hydroxy-2-deoxyguanosine, while also increasing the expression of heme oxygenase (HO-1) nuclear factor erythroid 2-related factor 2 (Nrf2) in TBI patients.

In another study, Gu *et al*. evaluated the preventive effects of AA on rat craniocerebral damage using the hydraulic shock method to produce an open model and the drop-weight method to create a closed model.[16] In all animal models of craniocerebral injury, AA successfully decreased the water content of brain tissue, enhancing the permeability of the compromised blood-brain barrier (BBB) and safeguarding brain tissue. In addition, in brain tissues from craniocerebral injuries, AA can successfully downregulate the expression of several inflammatory markers such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), indicating that AA can prevent craniocerebral injuries by reducing inflammation. Both of these studies corroborate our findings that *C. asiatica* offers protection against TBI.

Cinnamon is a spice that is most commonly used to season food. It has amazing qualities that have helped traditional medicine for millennia by reducing the symptoms of many diseases.[45] Among the bioactive substances found in cinnamon are eugenol, camphor, and trans-cinnamaldehyde.[18] Disorders of the neurological system and other illnesses linked to elevated levels of oxidants and proinflammatory biomarkers may benefit from cinnamon administration.[2] Due to its well-known cognitive enhancer and anti-amyloid properties, cinnamon exhibits neuroprotective activity by reducing inflammation and oxidative damage in TBI. It may also play a therapeutic role in dementia due to TBI.[50]

A study conducted by Qubty *et al*.[35] shows that consuming cinnamon extract (CE) both before and after a TBI can lessen the injury's associated cognitive deterioration. There are also decreases in visual and spatial memory, which may be mitigated by CE usage. Most importantly, IHC results corroborate their behavioral tests: Mice that ingested CE exhibited notably reduced neuronal damage in the hippocampus's dentate gyrus and temporal cortex, demonstrating that the application of the cinnamon fraction considerably enhances neuronal survival after TBI. These findings may pave the way for improved care for people with cognitive impairments or those attempting to recover from brain injuries.

According to another study by Yulug *et al*.,[50] male mice exposed to cold shock had their TBI affected by cinnamon polyphenol extract. The well-known activator of endogenous anti-oxidative pathways, Nrf2, was greatly elevated by cinnamon. In addition, cinnamon substantially raised levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase while lowering brain Malondialdehyde (MDA) levels. Cinnamon stimulated the body's natural antioxidant defense systems and markedly reduced the expression of cytokines. By reducing inflammation and oxidative damage, CE therapy prevented injury-induced neuronal death and enhanced the histological results of TBI. These two studies support our findings that CE protects against TBI.

Spirulina is a popular dietary supplement that is high in antioxidants and proteins. The blue-green algae spirulina is high in proteins, vital fatty acids, vitamins, and minerals. Spirulina is rich in minerals such as manganese, zinc, copper, iron, and gamma-linolenic acid (an important fatty acid), and it includes 60–70% protein by weight. Vitamin B12 is particularly abundant in Spirulina. It also contains a variety of antioxidants, including flavonoids, provitamin A (beta-carotene), Vitamin C, E, selenium, and phycocyanin, as well as SOD, which has been shown to have antioxidant potential in numerous *in vivo* and *in vitro* tests.[7,38,44]

According to a study by Thaakur and Sravanthi[42] in male albino rats, pretreatment with spirulina (90, 180 mg/kg) considerably reduced the neurological deficit. Spirulina 45 and 90 mg/kg pretreatment results in neural cell degeneration, minor congestion, and slight vaculations, respectively, while spirulina 180 mg/kg results in neuronal cells with a normal nucleus. Pretreatment dose-dependently corrected blood vessel congestion, congestion, and necrotic degeneration of neural cells. This outcome is consistent with our studies as well.

GFAP is a protein that is primarily found in astrocytes (AS) or glial cells, and its presence can induce activation of AS.[51] When the brain is damaged, GFAP is released from brain cells into the interstitial fluid and peripheral circulation through BBB.[19] IHC studies in animal models have demonstrated that the number of glial cells and levels of GFAP increase alongside the severity of brain injury.[10,34,51] From the IHC results in our study, it showed a positive stain of neuronal

GFAP antibody in the experimental group. This suggests that *C. asiatica*, cinnamon, and spirulina possess neuroprotective properties, as they reduce the severity of brain damage.

Ho *et al*., 2013,[21] demonstrated the neuroprotective properties of cinnamon, particularly its main component, cinnamaldehyde, in reducing microglial activation and neuroinflammation. The primary quantitative outcomes revealed a significant reduction in inflammatory markers such as IL-1b, IL-6, TNF-a, and NO on findings in cinnamon's inhibition of these markers at 50 lg/mL in BV2 microglial cells. BV-2 we were unable to define this term and we did not find it in the literature. This is the type of microgial cells.

In the study conducted by Chen *et al*. 2012,[9] the neuroprotective effects of Spirulina platensis and its active component, C-phycocyanin (C-PC), were explored in relation to their ability to modulate inflammatory responses in microglial cells. This research focused on BV-2 microglial cells treated with lipopolysaccharide (LPS) and different concentrations of Spirulina platensis water extract or C-PC for a period of 24 h. The study findings revealed that LPS significantly increased lactate dehydrogenase (LDH) production and upregulated the expression of inflammatory genes such as inducible NO synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, and IL-6. However, both Spirulina platensis water extract and C-PC markedly reduced the LPS-induced release of LDH and the expression of iNOS, COX-2, TNF-α, and IL-6 mRNA. These results underscore the potential of Spirulina platensis and C-PC as effective agents in reducing cytotoxicity and inhibiting the expression of key inflammation-related genes in LPS-stimulated BV-2 microglial cells, suggesting their utility in managing neuroinflammatory conditions.

Rochmah *et al*., 2019[39] investigated the neuroprotective effects of Centella asiatica on Sprague Dawley rats with chronic stress. The study specifically focused on histopathological findings, emphasizing the changes in the expression of key neuroinflammatory and neurotrophic markers within the hippocampus. The treatment with these natural compounds significantly altered the levels of these biomarkers, suggesting their potential benefits. For instance, treated rats displayed reduced levels of hippocampal tumor necrosis factor-alpha (TNF-α) compared to the control group. Additionally, the expression of brain-derived neurotrophic factor (BDNF) increased significantly, suggesting enhanced neuroprotection and recovery processes. This comprehensive study underscores the potential of these herbal extracts as therapeutic agents in managing and mitigating the effects through modulating critical biological pathways involved in inflammation and neuronal recovery.

Blaylock and Maroon, 2011,[6] further explored the role of microglia in TBI. Microglia are brain-innate immune cells that play a role in the activation of various pro-inflammatory cytokines and excitotoxins. This condition may worsen the brain damage that occurs and may increase the risk of progressive neurodegeneration in TBI. Moreover, the interaction between proinflammatory cytokine receptors and glutamate receptors on activated microglia can create a chronic neurodegenerative cycle, in which inflammatory cytokines and excitotoxins stimulate each other's release, exacerbating brain injury. This brain damage process can be a potential therapeutic target of Centella Asiatica, Cinnamon, and Spirulina as substantial neuroprotectors, highlighting their utility in potentially enhancing TBI recovery protocols. Such natural compounds could offer a complementary approach to traditional treatments, emphasizing the importance of further research into their mechanisms of action and long-term benefits in TBI recovery.

## CONCLUSION

This study showed that the effect of giving *C. asiatica*, cinnamon, and spirulina on the histopathological findings of the brain of SD rats with TBI could protect the brain (neuroprotective) in the acute phase. *C. asiatica*, cinnamon, and spirulina can increase GFAP antibody expression in neuron-supporting cells in the acute phase (neuroprotective). There is a correlation between GFAP in histopathological findings and *C. asiatica*, cinnamon, and spirulina.

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### Ethical approval

The Institutional Review Board approved the research/study at the Ethical Committee of the Faculty of Medicine, Universitas Mataram, number 048/UN17.F7/ETIK/2023, dated February 16, 2023.

### Declaration of patient consent

Patient's consent 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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