

Effect of *Centella Asiatica* (L.) Extract on Serum Levels of IL-6 and IL-10 in Traumatic Brain Injury Rat

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Abstract

Introduction: Traumatic brain injury (TBI) represents a major global health burden, because it is the foremost causes of death, particularly in young adults. Elevated IL-6 and IL-10 serum levels in severe TBI have been identified as an early indicator of unfavorable clinical outcomes. Pegagan (*Centella asiatica* (L.)) has antioxidant, neuroprotective, neurogenerative, anti-inflammatory properties. Our goal of this study was to find out what happened to IL-6 and IL-10 levels in blood of the TBI rat model when they were given pegagan extract (*Centella asiatica* (L.)).

Subject and Method: experimental research design. For 3 days, there were 4 groups of male Wistar strain rats (*Rattus norvegicus*) subjects, consisting of three treatment groups (pegagan extract doses of 300 mg/kgBW, 500 mg/kgBW, and 1000 mg/kgBW) and one control group. On the 4th day, blood was taken, and we continued to examine IL-6 and IL-10 serum levels by ELISA.

Result: A dose-dependent and significant increase of IL-6 and IL-10 serum levels was observed in the treatment groups compared with control group.

Conclusion: In TBI rat model, administration of pegagan (*Centella asiatica* (L.)) extract increases IL-6 and IL-10 levels.

Key words: *Centella asiatica* (L.), IL-6, IL-10, Traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is still a health challenge around the world. It causes death, particularly in the case of young adults, but it can also be resulted in enduring consequences such as physical, cognitive, behavioral, and emotional impairment.¹ Two mechanisms determine the outcome of a head injury: a primary insult resulting from the mechanical strain on the skull and brain during impact, and secondary injuries resulting from the primary wound.² Secondary injury causes the majority of brain damage at TBI.³ Cellular mediators like pro-inflammatory

cytokines, prostaglandins, free radicals, and complements are released when there are primary and secondary injuries. This causes immune and glial cells to move into brain tissue and cause inflammation. Any inflammatory response that arises within the brain and spinal cord can be defined as neuroinflammation.⁴ Leukocytes that infiltrate tissue at both primary and secondary injury sites will secrete substantial amounts of pro-inflammatory cytokines, including IL-6, IL-1 β , and TNF- α . When microglia are activated, they release chemicals that cause inflammation (IL-1 β , IL-6, IL-12, IFN- γ , and TNF- α), chemicals that stop inflammation (IL-10 and TGF- β), and other chemicals that hurt neurons.⁵ elevated IL-6

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serum levels and a significant decrease in IL-10 levels in severe TBI. Increased serum IL-6 levels alongside reduced IL-10 concentrations can be biomarkers for early predictors of deteriorating clinical outcomes in severe.^{6,7}

Previous report showed that pegagan (*Centella asiatica* L.) can help decrease post-TBI inflammation by reducing the amount of TNF- α in the blood and increasing the amount of antiapoptotic protein Bcl-2.¹⁰ Pegagan (*Centella asiatica* (L.)) is an herbal plant that has the main compounds, namely asiatic acid, madecassoside acid, madecassoside, asiaticoside, alkaloids, glucosides, flavonoids, and other phenolic compounds.⁸ These compounds have benefits as anti-inflammatory, neuroprotective, neurogenerative and antioxidants.⁹ Our study aimed to assess pegagan extract (*Centella asiatica* (L.)) effect IL-6 and IL-10 serum levels in TBI in a rat model.

Subject and Method

This research was conducted at the Environmental Laboratory, Plant Physiology Laboratory, Animal and Research Laboratory, Faculty of Medicine, Jenderal Soedirman University, from October 2023 to January 2024. The research design used Post-Test Only Controlled Group True Experimental Design with experimental animals of white Wistar rats (*Rattus Norvegicus*) and the inclusion criteria of white Wistar rats, male, 2-3 months old, weighing 150–200 grams, healthy, and active. Exceptions to rats that are sick or die during acclimatization. Four groups were identified to determine these mice, with each group containing 8 mice : group 1 (P1) were TBI model mice without administration of pegagan extract (*Centella asiatica* (L.)); group 2 (P2) were TBI model mice given pegagan extract (*Centella asiatica* (L.)) 300mg/kgBW/day; group 3 (P3) were TBI model mice given pegagan extract (*Centella asiatica* (L.)) 500 mg/kgBW/day, and group 4 (P4) were TBI model mice given pegagan extract (*Centella asiatica* (L.)) 1000 mg/kgBW/day. All protocols related to these experimental animals have been approved by the Research Ethics Committee of the Faculty of Medicine,

Jenderal Soedirman University (017/KEPK/PE/VI/2024).

A total of 32 mice that will be used as TBI models are kept and acclimatized for 7 days according to the standards for maintaining experimental animals in the Animal and Research Laboratory of Jenderal Soedirman University. Before being treated, the mice were lightly anesthetized, the fur on their heads were shaved and cleaned with 70% alcohol. After the mice were anesthetized, they were placed on a flat surface and then the head and their four legs were fixed. The creation of TBI model mice was carried out using the Weight Drop Injury (WDI) method, where a 50-gram iron cylinder (10 mm diameter) was dropped once at a 90-degree angle from a height of 50 cm right on the midcoronal plate between bregma and lambda at the sagittal suture (midline injury). The extract was given after the mice recovered from the effects of anesthesia This research was conducted at the Environmental Laboratory, Plant Physiology Laboratory, Animal and Research Laboratory, Faculty of Medicine, Universitas Jenderal Soedirman, from October 2023 to January 2024. The research design used Post-Test Only Controlled Group True Experimental Design with experimental animals of white Wistar rats. Inclusion criteria consisted of healthy, active rats aged 2–3 months and weighing between 150–200 grams. Exceptions to rats that were sick or die during acclimatization. Four groups were identified to determine these mice, with each group containing 8 mice: group 1 (P1) were TBI model mice without administration of pegagan extract; group 2 (P2) were TBI model mice given pegagan extract 300mg/kgBW/day; group 3 (P3) were TBI model mice given pegagan extract 500 mg/kgBW/day, and group 4 (P4) were TBI model mice given pegagan extract 1000 mg/kgBW/day. All experimental procedures involving animals were approved by the Faculty of Medicine Ethics Commiteettee, Universitas Jenderal Soedirman (017/KEPK/PE/VI/2024).

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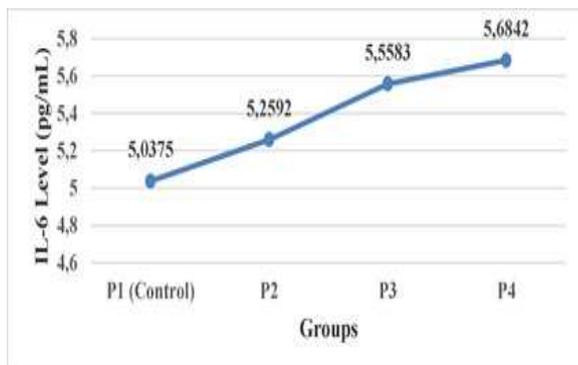


Figure 1. IL-6 serum levels (pg/mL).

between bregma and lambda at the sagittal suture (midline injury). The extract was given after the mice recovered from the effects of anesthesia.

The pegagan (*Centella asiatica* (L.) simplicia) was made by washing pegagan thoroughly, cutting it into small pieces, and dried it in an oven at a temperature of 50 °C. The obtained simplicia was finely ground and subsequently macerated in 96% ethyl acetate for 24 hours. The resulting filtrate was then re-macerated using 96% ethyl acetate and allowed to stand for an additional 24 hours. The resulting extract was solidified

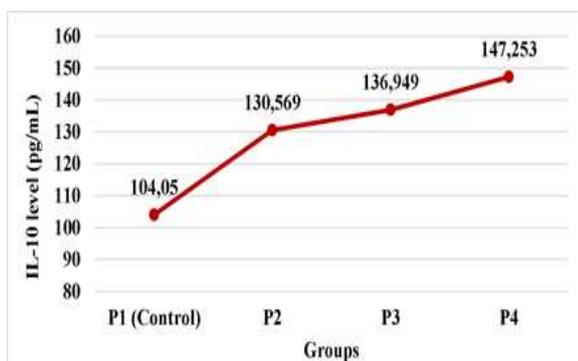


Figure 2. Diagram of IL-10 levels (pg/mL)

by a rotary evaporator at 40 °C until a viscous consistency was achieved. The extract was by further dried in a water bath at 60 °C to obtain a thick extract. The extract was dissolved with distilled water and was ready to use. The extract was administered to experimental animals orally using a nasogastric tube once a day for 3 days with doses of 300, 500, and 1000 mg/kg body weight per day for groups 2, 3, and 4, respectively. On the 4th day, the blood samples were collected from orbital sinus vein and centrifuged at 2,500 rpm for 15 minutes. The obtained serum was then examined for IL-6 and IL-10 serum levels using ELISA from the Bioassay Technology Laboratory (BT Lab). The obtained data were subjected to descriptive analysis by determining the mean and standard deviation and illustrated through the form of images. The Shapiro- Wilk test was used as normality test, and the Levene test was used as a homogeneity test. The ANOVA test was used to examine the hypothesis of serum IL-6 and IL-10 levels, and to identify specific group differences, Tukey Post Hoc test was used, with values established statistically significant at p -value <0.05

Result

The results of serum level of IL-6 can be seen on figure 1. Group P1 had a mean of 5.037 pg/mL, while P4 had the highest mean of 5.684 pg/mL. The mean serum IL-6 levels of the four groups were significantly different, proven by the One Way Anova test ($p = 0.021$, $p \leq 0.05$). Based on the analysis with the Post-hoc Tukey follow-up test, a significant difference was obtained between P4 and P1 ($p = 0.005$); between P3 and P1 ($p = 0.024$). The results of IL-10 serum levels can be seen in figure 2. Group P4 had the highest mean of 147.253 pg/ mL, the lowest mean of P1 was 104.050 pg/ mL. Significant differences between groups with IL-10 levels obtained have been proven by the One Way Anova test, ($p = 0.043$, $p \leq 0.05$). Based on the analysis with the Post-hoc Tukey follow-up test, a significant difference was obtained between P4 and P1 ($p = 0.007$); between P3 and P1 ($p = 0.024$).

Discussion

Our study showed administration of different doses of pegagan (*Centella asiatica* (L.)) extract increased IL-6 and IL-10 serum levels in TBI rat model after 3 days. The increase in serum showed a dose- dependent pattern, where the higher the dose of pegagan (*Centella asiatica* (L.)) given, the higher the IL-6 and IL-10 serum levels obtained.

Interleukin -6

Interleukin 6 (IL-6) is a pro-inflammatory cytokine generated in reaction to infection or tissue injury, released by microglia, astrocytes, and neurons after TBI. After TBI, cell damage that occurs will be recognized as an antigen by Antigen Presenting Cell (APC). MHC II presented by APC will be recognized by CD4+ T cells (Th), leading to differentiation into T helper 1 (Th1) and 2 (Th2) cells. Th1 cells not only secrete IL-2 and IFN- γ , but will also initiate macrophages to release pro-inflammatory cytokines, including IL-1, IL-6, IL-8 and TNF- α from microglia cells. T helper 2 cells (Th2) will produce IL-6.¹¹ Dosage administration of pegagan extract is expected to lower IL-6 levels through PPAR γ activation and NF κ B signal pathway inhibition. Supported by the study of Hao et al., that in vivo and in vitro, the asiatic acid in pegagan (*Centella Asiatica* (L.)) is significantly inhibited the inflammatory response induced by LPS, which was characterized by decreased production of PGE2, NO, IL-6, and IL-8, through PPAR γ activation and inhibition of NF κ B signaling pathway. Contrary to theory, this study found a dose-related elevation in IL-6 levels. Therefore, we can conclude that the administration of the pegagan (*Centella Asiatica* (L.)) did not lower the level of IL-6 in the study. The elevated IL-6 levels in this study could be caused by increased macrophage activity due to infection, inflammation, or antigen stimulation. One consideration for this is that IL-6 functions not only in the inflammatory process, but also in immunity.¹³

Madecassoside and asiaticoside are an immunostimulant that can increase macrophage phagocytosis activity. Activated macrophages are capable of secreting cytokines, including IL-1, IL-4, IL- 6, and TNF- α . Earlier study

demonstrated that administering the pegagan (*Centella Asiatica* (L.)) extract to mice that had been inoculated with *S. typhi* resulted in a significant elevation of IL-6 levels.¹⁴ These mice had the highest amounts of IL-6 when they were given 500 mg/kg extract. The extract activates macrophages, increasing their responsiveness to the antigen, triggering immediate migration and phagocytosis upon antigen stimulus.¹⁵ Through the secretion of pro- inflammatory cytokines, such as IL-1, IL-4, IL-6, TNF- α alongside phagocytic activity, macrophages play a crucial role in resolving inflammation. The inflammatory reaction begins when receptors on innate immune cells detect specific molecular patterns associated with pathogens or cellular stress. These molecular patterns, known as Pathogen-Associated Molecular Patterns (PAMPs), are derived from microorganisms and are detected by Pattern Recognition Receptors (PRRs) present on immune cells.^{16,17}

Immune receptors that play crucial role in recognition and response of host cells to microbial pathogens are Toll-like receptors (TLRs). When the cell surface expresses Toll-2, -4, and -5 receptors, which recognize bacterial components recognize the signal it will activate the downstream signal cascade through Myeloid Adaptor proteins such as Myeloid Differentiation Primary Response 88 (MyD88) and Toll/ Interleukin-1 Receptor (TIR) domain-containing adaptor inducing interferon- β (TRIF) activate transcription factors like NF- κ B, which in turn induce the expression of pro-inflammatory mediators such as IL-6 and TNF- α .¹⁶ Interleukin 6 also has a role as a regulator and mediator of dendritic cells in immune response and inflammation. When dendritic cells are activated in living things, they can keep produce cytokines or chemokines like IL-12, IL-6, IL-10, and CCL16. They can also help T cells and others to sites of infection or inflammation. Dendritic cells, as key components of the immune system, serving as APC cells that present antigens to B and T cells.¹³ The theory above suggests that antigen exposure can activate dendritic cells, leading to elevated IL-6 level in this study An elevated IL-6 levels in this study could also link to

the neurogenesis process and its neuroprotective benefits. Several cytokines, inflammatory factors, neurotransmitters, and neuropeptides influence the regulation of IL-6 within brain cells. Glial cells and nerve cells, especially the sympathetic and sensory ganglia, can express IL-6 and IL-6R at various levels throughout the brain. In vitro, microglia, astrocytes, and the N18 nerve line express IL-6, while in vivo, oligodendrocytes can express IL-6. Membrane depolarization could be one of the major mechanisms of IL-6 neuronal upregulation. The NMDA glutamate agonist and the Ca²⁺/calmodulin-dependent kinase play a big role in this. The AMPc-PKA pathway can also induce astrocytic IL-6.¹⁵ Although increased levels of IL-6 in TBI can cause excessive brain damage, IL-6 plays a neuroprotective role by enhancing post-traumatic healing.

This refers to the dual role of IL-6, which is both anti-inflammatory and neuroprotective. At the cellular level, IL-6 can improve neuronal differentiation and post-injury survival through several mechanisms, including the suppression of TNF- α , synthesis of NGF (Nerve Growth Factor), and modulation of NMDAR mediated by exotoxicity. IL-6 inhibits neuronal apoptosis in the brain by activating STAT 3 in the JAK/STAT pathway, providing a neuroprotective effect. Interleukin 6 can also decrease MPO activity, reducing the regulation of inflammatory sites such as TNF- α and IL-1 β . In addition to inhibiting TNF-synthesis and inducing NGF production, IL-6 also regulates neuronal differentiation and survival, reduces neuronal excitability by inhibiting voltage-gated sodium channels, and protects against glutamate-induced neurotoxicity. In the preclinical TBI model, mice with IL-6 deletion showed increased mortality, decreased recovery, cerebral vascular leakage, motor behavioral deficits and inflammatory response disorders, declining astrogliosis and reduced regeneration, increased oxidative stress, and apoptosis.^{13,17}

Interleukin - 10

The increase in IL-10 levels when administering multiple doses of pegagan (*Centella Asiatica* (L.))

on TBI models of rat in this study can be assumed to be positive. Increased levels of IL-10 post TBI will suppress the neuroinflammatory reactions that occur and increase the survival of neurons, resulting in a more comprehensive inhibition of neuroinflammatory reactions thereby improving the survival of neurons. Interleukin 10 functions as an anti-inflammatory cytokine that modulates the outcome of TBI by facilitating inflammatory cascade resolution. The presence of resident CNS immune surveillance glial cell activation, which releases cytokines, chemokines, and other immunological mediators, characterizes neuroinflammation. This activation facilitates the migration of peripheral immune cells such as monocytes, neutrophils, and lymphocytes. This response will help repair damaged tissue. Not only does IL-10 is crucial in the inflammatory process, but it also plays a critical role during the resolution process. Brain cells that make more IL-10 will be able to stay alive longer, and the inflammatory response will be reduced. This happens through a number of signal pathways, including NF κ B being downregulated.¹⁸

The p38 pathway regulates IL-10 regulation by activating the transcription factor sp1, which is induced by TNF- α via the NF κ B-dependent pathway. Upon binding to its receptors (IL-10R1 and IL-10R2), IL-10 activates the STAT3 signaling cascade, such as Suppressor of Cytokine Synthesis (SOCS-3), which in turn downregulates pro-inflammatory cytokines, including IFN, TNF, IL-2, IL-3, IL-4, and GM-CSF, as well as chemokines, APCs, and costimulatory molecules. By activating the phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K)/Akt pathway through other signaling pathways, IL-10 prevents apoptosis by upregulating Bcl-2 and Bcl-xl, while inhibiting caspase-3. Previous research stated that IL-10 deficiency can worsen motor and cognitive dysfunction induced by TBI, worsen inflammation, cerebral edema and apoptosis and cancel the therapeutic benefits of HBO in TBI mice model.¹⁹ In the study, IL-10 levels were 10.5 pg/mL, lower than IL-10 levels in group P1 (control) in this study. This difference may be caused by changes in the type of injury produced or from the type of TBI model used.

Measurement of IL-10 levels in severe TBI patients by previous study, showed a decrease in 72 hours post-trauma, namely 3 pg/ mL (24 hours post TBI) and 2.8 pg/mL (72 hours post TBI). In TBI patients who died, the IL-10 levels obtained tended to increase, namely 8 pg/ mL at 24 hours post TBI, and 10 pg/mL at 72 hours post TBI.¹⁹ The measurement results are still much smaller than the IL-10 level measurements in groups P1 and P4. This difference can be caused by differences in the experimental object model, factors causing TBI and other factors that affect the subject's condition, for example comorbidities or risk factors.

Pegagan (*Centella asiatica* (L.)) is reported to reverse nerve injury through antioxidant activity, prevent apoptosis, and increase cell survival by blocking the NOD2/MAPK/TLR4/MyD88/NFκB signaling pathway. The antioxidant properties of pegagan (*Centella asiatica* (L.)) are useful for weakening oxidative stress, regenerative neurons, preventing neuron damage, inhibiting neurotoxicity, preventing Al Zheimer's, anti- anxiety and anti-depression. The pathway used is through the GABAergic system, inhibition of acetylcholinesterase (AChE) activity, and a reduction in amyloid plaque accumulation by modulating the secretory enzyme.²⁰ Glutamate amino acid as a precursor of Gamma Aminobutyric Acid (GABA) formation in pegagan is thought to function as an excitatory neurotransmitter that can increase the expression of Brain Derived Neurotrophic Factor (BDNF) which is a crucial neurotrophin that plays an important role in the survival, development, and growth of neurons. It also contributes to long-term memory, synaptic plasticity and can improve cognitive function.³ Other studies also mentioned an increase in dendritic arborization of hippocampal CA3 neurons in vivo in the administration of pegagan followed by induction of changes in dendritic morphology of the substantia nigra of experimental animals.⁴

Conclusion

Our study showed that administration of pegagan (*Centella asiatica* (L.)) in ethyl acetate doses

of 300mg/kgBW, 500mg/kgBW and 1000mg/kgBW can significantly increase IL-6 and IL-10 serum levels in TBI mice model. Increased serum levels can occur due to increased macrophage activity triggered by the natural content of pegagan (*Centella asiatica* (L.)) and due to increased neuroprotective activity in the CNS triggered by tissue damage in the brain.

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