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The Effect of Papua Red Fruit Extract (*Pandanus conoideus*) on TNF-α (Tumour Necrosis Factor-alpha) and IL-6 (Interleukin-6) Levels in a Mouse Model of Head Injury

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Abstract

Background: Head injury induces secondary inflammatory responses characterised by increased levels of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). *Pandanus conoideus* contains bioactive compounds with antioxidant and anti-inflammatory properties that may attenuate post-traumatic inflammation. **Aim:** To evaluate the effect of *P. conoideus* extract on serum IL-6 and TNF-α levels in a rat head-injury model. **Methods:** A laboratory-based experimental study was conducted using rats randomly assigned to a healthy control (HC), head injury control (SC), positive control (PC), and treatment groups receiving *P. conoideus* extract at doses of 100 mg/kg BW (EBM1), 200 mg/kg BW (EBM2), and 400 mg/kg BW (EBM3). Serum IL-6 and TNF-α levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA). Data were analysed using one-way Analysis of Variance (ANOVA) followed by post hoc testing. **Results:** Head injury significantly increased serum IL-6 and TNF-α levels compared with the healthy control group. Treatment with *P. conoideus* extract significantly reduced both IL-6 ($p = 0.010$) and TNF-α ($p = 0.005$) levels compared with the untreated head injury group. The greatest reductions were observed in the EBM3 group, indicating a dose-dependent anti-inflammatory effect of the extract. **Conclusion:** *P. conoideus* extract effectively reduced serum IL-6 and TNF-α levels in rats with head injury, with the 400 mg/kg BW dose producing the greatest anti-inflammatory effect.

Major Finding: These findings support the potential of *P. conoideus* extract as a promising natural candidate for further preclinical development in the management of post-traumatic neuroinflammation.

Keywords: Head Injury, IL-6, *Pandanus conoideus*, TNF-α, Traumatic Brain Injury

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1. Introduction

Head injury is a serious medical condition that poses substantial challenges to both individuals and healthcare systems worldwide[1]. It refers to any form of damage affecting the head region, including the scalp, skull, and brain tissue, commonly resulting from physical trauma such as traffic accidents, falls, or violent incidents[2]. In addition to causing significant clinical problems, head injury also imposes a substantial economic and social burden through high treatment costs, loss of productivity, the need for long-term rehabilitation, and psychological distress experienced by patients' families[3,4]. Current management strategies for head injury have involved multidisciplinary approaches; however, clinical outcomes in many cases remain unsatisfactory, particularly in cases complicated by secondary inflammatory responses[5,6].

In head injury, tissue damage occurs not only as a result of the primary trauma but also progresses through secondary injury mechanisms involving oxidative stress, glial cell activation, disruption of the blood-brain barrier, and the release of inflammatory mediators[7]. Among the mediators that play critical roles in this process are Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). These proinflammatory cytokines are predominantly produced by immune cells, particularly macrophages, and contribute to inflammatory processes that exacerbate tissue damage[8,9]. TNF-α has been recognised as a key mediator of cellular apoptosis and tissue injury, whereas IL-6 contributes to the amplification of the inflammatory response. Elevated levels of TNF-α and IL-6 in head injury have also been associated with more severe brain tissue damage, prolonged recovery, and poorer neurological outcomes[10,11].

The activation of microglia and astrocytes following traumatic injury triggers the release of various proinflammatory mediators, which subsequently increase blood-brain barrier permeability and exacerbate neuroinflammation. An uncontrolled inflammatory response may lead to cerebral oedema, secondary neuronal damage, and an increased risk of long-term neurological complications. Therefore, modulation of post-traumatic inflammatory processes has become one of the major therapeutic targets in efforts to improve the prognosis of head injury[12].

One potential approach involves the use of natural products as complementary therapy. *P. conoideus*, commonly known as Papuan red fruit (Figure 1), is an endemic Indonesian plant that has long been traditionally utilised and is known to be rich in carotenoids, tocopherols, β-carotene, α-tocopherol, and various fatty acids, including oleic acid, linoleic acid, linolenic acid, and decanoic acid[13,14].

These bioactive compounds are associated with antioxidant activity that may help neutralise free radicals and protect cells against oxidative damage. In addition, *P. conoideus* (Papuan red fruit) has also been reported to exhibit anti-inflammatory potential through its flavonoid, alkaloid, steroid, triterpenoid, and carotenoid contents, which may suppress inflammatory pathways, including NF-κB activation, and reduce the production of inflammatory mediators such as interleukin-6 (IL-6), a cytokine that plays a pivotal role in the inflammatory process[16].

2. Materials and Methods

2.1 Experimental Animals

This study used male Wistar rats aged 8–10 weeks, weighing 200–250 g. The experimental animals were randomly selected and maintained under standard laboratory conditions with controlled temperature, humidity, and a 12 h light/dark cycle, with free access to standard pellet diet and water. The animals were acclimatised for seven days before the experiment. All experimental procedures were approved by the Health Research Ethics Committee, Faculty of Medicine, Jenderal Soedirman University (Ethical Approval No. 126/KEPK/PE/XI/2025) and were conducted in accordance with the ethical principles for laboratory animal research.



Figure 1. *Pandanus conoideus.*

2.2 Study Design

This laboratory-based experimental study employed a randomised post-test-only control group design. The rats were randomly allocated into six experimental groups. The healthy control (HC) group consisted of rats that received neither head injury induction nor *P. conoideus* extract. The traumatic brain injury control (SC) group consisted of rats subjected to head injury induction without receiving any treatment. The positive control (PC) group consisted of rats with experimentally induced traumatic brain injury treated orally with ibuprofen at a dose of 28.335 mg/kgBW. The EBM1, EBM2, and EBM3 groups consisted of rats with experimentally induced traumatic brain injury treated orally with *P. conoideus* extract at doses of 100, 200, and 400 mg/kgBW, respectively.

2.3 Research Subjects and Group Allocation

Following head injury induction, rats in the Positive Control (PC) group received ibuprofen orally by gavage at a dose of 28.335 mg/kgBW, while rats in the EBM1, EBM2, and EBM3 groups received *P. conoideus* extract orally by gavage at doses of 100, 200, and 400 mg/kgBW, respectively. All treatments were administered once daily for seven consecutive days. Rats in the Healthy Control (HC) and traumatic brain injury Control (SC) Groups received the vehicle according to the same administration schedule. At the end of the treatment period, blood samples were collected for serum TNF-α and IL-6 analysis.

2.4 Preparation of *Pandanus conoideus* Extract

Fresh fruits of *P. conoideus* were obtained from Papua, Indonesia. The plant material was taxonomically identified and authenticated by the Environmental Laboratory, Faculty of Biology, Jenderal Soedirman University, Indonesia. The identification was documented under Certificate No. B/514/UN23.6.10/TA.00.01/2025, issued on 24 November 2025, confirming the species as *P. conoideus* Lam. After cleaning, drying, and pulverisation, the powdered material was extracted using 96% ethanol and n-hexane to obtain a concentrated extract. The extract was then prepared for oral administration at doses of 100, 200, and 400 mg/kgBW. Before administration, phytochemical screening was performed using Thin-Layer Chromatography (TLC) to identify the presence of bioactive compounds. The doses of *P. conoideus* extract (100, 200, and 400 mg/kgBW) were selected based on previous experimental[17].

2.5 Head Injury Induction

Head injury was induced in the SC, PC, EBM1, EBM2, and EBM3 groups using a closed blunt head injury model. Briefly, a 50 g weight was dropped from a height of 80 cm onto the cranial region of each rat to induce traumatic brain injury according to the established experimental protocol. This model has been widely used to produce reproducible traumatic brain injury and the subsequent inflammatory response. Rats in the Healthy Control (HC) group were not subjected to head injury induction.

2.6 Treatment Administration

Following head injury induction, rats in the Positive Control (PC) group received ibuprofen orally by gavage at a dose of 28.335 mg/kgBW, while rats in the EBM1, EBM2, and EBM3 groups received *P. conoideus* extract orally by gavage at doses of 100, 200, and 400 mg/kgBW, respectively. All treatments were administered once daily for seven consecutive days. Rats in the Healthy Control (HC) and traumatic brain injury Control (SC) Groups received the vehicle according to the same administration schedule.

2.7 Sample Collection

On day 7 after the treatment period, blood samples were collected from all rats via the retro-orbital plexus under appropriate anaesthesia. The samples were transferred into collection tubes and centrifuged to obtain serum, which was stored at −20 °C until analysis. Serum levels of Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) were subsequently determined.

2.8 Measurement of TNF-α and IL-6 Levels

2.8.1 Quantitative Assessment of TNF-α Levels

TNF-α levels (pg/mg) were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit. The assay was performed using the sandwich enzyme immunoassay method, and sample concentrations were determined based on the generated standard curve.

2.8.2 Quantitative Assessment of IL-6 Levels

IL-6 levels (pg/mg) were measured in tissue homogenates using an Enzyme-Linked Immunosorbent Assay (ELISA) kit. The assay was conducted using the sandwich enzyme immunoassay method, and sample concentrations were determined based on the standard curve.

2.9 Statistical Analysis

Data obtained from the measurement of TNF-α and IL-6 levels were statistically analysed using one-way Analysis of Variance (ANOVA) to determine differences in mean values among groups. When a significant difference was identified, the analysis was followed by Tukey's post hoc test to evaluate differences between treatment groups. Statistical significance was established at $p < 0.05$.

3. Results

3.1 Assessment of IL-6 and TNF-α Levels

Table 1 presents the serum IL-6 and TNF-α levels in the experimental groups. The results demonstrated differences in IL-6 and TNF-α levels among the treatment groups. Regarding the IL-6 parameter, the traumatic brain injury (SC) group exhibited the highest level compared with the other groups, reaching 7.63 ± 0.85 ng/mL, whereas the lowest level was observed in the EBM3 group at 5.03 ± 0.49 ng/mL. The Healthy Control (HC) group showed an IL-6 level of 5.65 ± 0.54 ng/mL, while the PC, EBM1, and EBM2 groups demonstrated levels of 6.44 ± 1.85 ng/mL, 6.66 ± 0.50 ng/mL, and 5.26 ± 0.62 ng/mL, respectively. Statistical analysis revealed that the differences in IL-6 levels among groups were statistically significant ($p = 0.01$).

For the TNF-α parameter, the SC group likewise demonstrated the highest level, reaching 177.5 ± 35.57 ng/mL, whereas the lowest level was observed in the HC group at 110.0 ± 31.93 ng/mL. TNF-α levels in the PC, EBM1, EBM2, and EBM3 groups were 131.7 ± 32.00 ng/mL, 161.0 ± 4.84 ng/mL, 135.6 ± 10.44 ng/mL, and 119.5 ± 17.04 ng/mL, respectively. Statistical analysis indicated that the differences in TNF-α levels

Table 1. Serum IL-6 and TNF-α levels in Healthy Control rats (HC), traumatic brain injury control rats (SC), Positive Control rats treated with ibuprofen (PC), and traumatic brain-injured rats treated with *P. conoideus* extract at doses of 100 mg/kgBW (EBM1), 200 mg/kgBW (EBM2), and 400 mg/kgBW (EBM3)

Groups	Mean ± SD (ng/mL)			
	IL-6	P-value	TNF-α	P-value
HC	5.65 ± 0.54	0.01	110.0 ± 31.93	0.005
SC	7.63 ± 0.85		177.5 ± 35.57	
PC	6.44 ± 1.85		131.7 ± 32.00	
EBM1	6.66 ± 0.50		161.0 ± 4.84	
EBM2	5.26 ± 0.62		135.6 ± 10.44	
EBM3	5.03 ± 0.49		119.5 ± 17.04	

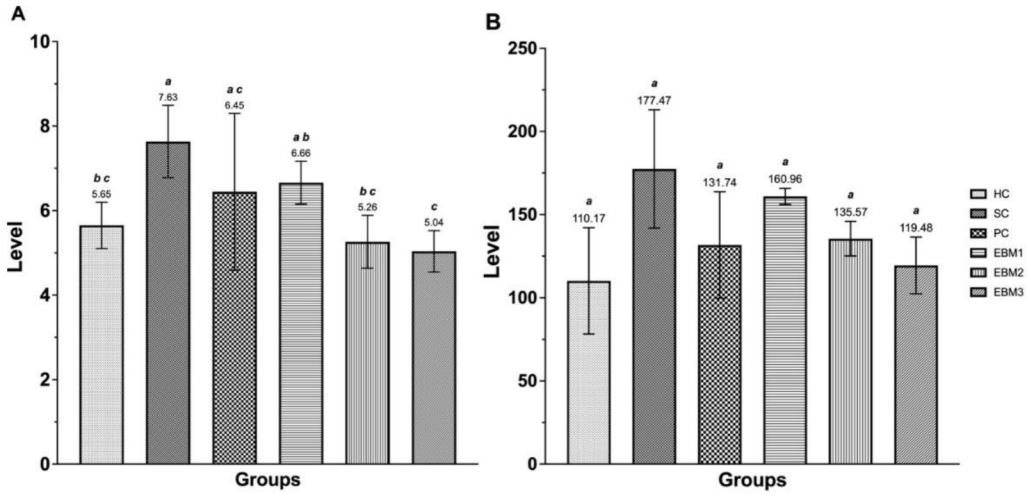


Figure 2. Post hoc analysis of serum IL-6 and TNF-α levels in healthy control rats (HC), traumatic brain injury control rats (SC), positive control rats treated with ibuprofen (PC), and traumatic brain-injured rats treated with *P. conoideus* extract at doses of 100 mg/kg BW (EBM1), 200 mg/kg BW (EBM2), and 400 mg/kg BW (EBM3).

among groups were also statistically significant (p = 0.005). Overall, administration of *P. conoideus* extract at higher doses showed a tendency to reduce IL-6 and TNF-α levels compared with the SC group, with the most pronounced effect observed in the EBM3 group.

3.2 Post Hoc Analysis of IL-6 and TNF-α Levels

Figure 2 illustrates the results of the post hoc analysis comparing IL-6 and TNF-α levels among the experimental groups. Post hoc analysis was performed to evaluate pairwise differences in IL-6 and TNF-α levels. The traumatic brain injury Control (SC) Group exhibited higher IL-6 and TNF-α levels than the Healthy Control (HC) group and the groups treated with *P. conoideus* extract. The EBM2 and EBM3 groups showed a greater reduction in pro-inflammatory cytokine levels than the EBM1 group, suggesting a dose-dependent anti-inflammatory effect of the extract. These findings are consistent with the primary analysis and indicate that *P. conoideus* extract attenuated the inflammatory response following traumatic brain injury.

4. Discussion

Head injury is a condition that triggers a cascade of secondary injury mechanisms, including oxidative stress, blood–brain barrier disruption, glial cell activation, and the release of inflammatory mediators. Among the mediators that play crucial roles in this process are Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), both of which are known to increase following trauma and contribute to the progression of brain tissue damage. Therefore, the search for therapeutic agents capable of suppressing post-traumatic inflammatory responses has become increasingly important to support improved clinical outcomes. *P. conoideus* has attracted considerable attention due to its bioactive compounds with potential antioxidant and anti-inflammatory properties. This study aimed to evaluate the effect of *P. conoideus* extract administration on IL-6 and TNF-α levels in a rat head-injury model. This study also expands previous findings regarding the modulatory effects of natural plant extracts on inflammatory biomarkers[18].

The findings of this study demonstrated that the head injury group exhibited higher IL-6 and TNF-α levels compared with the healthy control group. IL-6 levels in the SC group reached 7.63 ± 0.85 ng/mL, which was higher than those observed in the HC group (5.65 ± 0.54 ng/mL), with statistically significant differences among groups (p = 0.01). Similarly, TNF-α levels in the SC group were 177.5 ± 35.57 ng/mL, exceeding those in the HC group (110.0 ± 31.93 ng/mL), with a p-value of 0.005. These findings indicate that the induction of head injury in this study successfully triggered a systemic inflammatory response, as reflected by the elevation of these two major proinflammatory biomarkers.

The elevation of IL-6 and TNF-α levels in the head injury group is associated with post-traumatic oxidative stress mechanisms. Mechanical trauma disrupts cellular metabolism, induces tissue hypoxia, and causes mitochondrial dysfunction, which subsequently enhances the generation of Reactive Oxygen Species (ROS). Excessive ROS production further activates proinflammatory transcription pathways such as NF-κB, leading to increased expression of proinflammatory cytokines, including TNF-α and IL-6. TNF-α acts as an early inflammatory mediator that can exacerbate tissue damage and stimulate the release of additional inflammatory mediators, whereas IL-6 contributes to the amplification and persistence of the inflammatory response. Therefore, the elevated TNF-α and IL-6 levels observed in the SC group in this study reflect the activation of oxidative stress–inflammatory pathways following head injury.

In this study, administration of *P. conoideus* extract demonstrated a tendency to reduce IL-6 and TNF-α levels compared with the SC group. IL-6 levels decreased from 6.66 ± 0.50 ng/mL in the EBM1 group to 5.26 ± 0.62 ng/mL in the EBM2 group and further to 5.03 ± 0.49 ng/mL in the EBM3 group. A similar pattern was observed for TNF-α levels, which declined from 161.0 ± 4.84 ng/mL in the EBM1 group to 135.6 ± 10.44 ng/mL in the EBM2 group and 119.5 ± 17.04 ng/mL in the EBM3 group. These findings indicate a dose-dependent tendency, in which increasing doses of the extract were associated with greater reductions in inflammatory biomarkers. The EBM3 group demonstrated results most comparable to the healthy control group, suggesting that this dose exerted the strongest anti-inflammatory effect in the present study.

The reduction in IL-6 and TNF-α levels may be associated with the bioactive compounds present in *P. conoideus*, which contains carotenoids, tocopherols, β-carotene, α-tocopherol, and unsaturated fatty acids that function as antioxidants and protect cells against oxidative damage. In addition, Papuan red fruit also contains flavonoids, alkaloids, steroids, triterpenoids, and carotenoids, which have been reported to suppress inflammatory pathways, including the activation of the NF-κB transcription factor, as well as reduce inflammatory mediators such as IL-6[15].

Among these phytoconstituents, carotenoids and tocopherols are recognised as potent antioxidants that scavenge Reactive Oxygen Species (ROS), thereby limiting oxidative stress following traumatic brain injury. Reduced ROS production may prevent activation of the NF-κB signalling pathway, resulting in decreased transcription of pro-inflammatory cytokines, including TNF-α and IL-6[19]. In addition, flavonoids have been reported to inhibit Cyclooxygenase-2 (COX-2), inducible Nitric Oxide Synthase (iNOS), and Mitogen-Activated Protein Kinase (MAPK) signalling pathways, further suppressing inflammatory responses[20]. The combined actions of these phytoconstituents may therefore explain the dose-dependent reduction in IL-6 and TNF-α observed in the present study.

This mechanism is further supported by reports showing that *P. conoideus* extract can modulate ROS production in lipopolysaccharide-induced macrophages, thereby inhibiting the activation of inflammatory pathways such as NF-κB[21]. Although ROS and NF-κB were not directly measured in the present study, the reduction in IL-6 and TNF-α levels observed in the treatment groups may be associated with decreased oxidative stress and suppression of secondary inflammatory pathway activation following administration of *P. conoideus* extract. In other words, the antioxidant activity of Papuan red fruit may reduce ROS production, which in turn could attenuate NF-κB activation and ultimately decrease the expression of TNF-α and IL-6.

5. Conclusion

Head injury significantly increased serum IL-6 and TNF-α levels, indicating the induction of a systemic inflammatory response in the rat model. Administration of *P. conoideus* extract reduced both IL-6 and TNF-α levels in a dose-dependent manner compared with the untreated head injury group, with the 400 mg/kg BW dose producing the greatest anti-inflammatory effect and cytokine levels closest to those of the healthy control group. These findings suggest that *P. conoideus* extract may serve as a promising natural candidate for attenuating post-traumatic neuroinflammation. Further studies are warranted to elucidate the underlying molecular mechanisms and evaluate its long-term efficacy and safety.

6. References

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Author Contribution

Kamal Agung Wijayana: Conceptualisation, methodology, supervision, writing and editing. Wahyudin: Conceptualisation, methodology, investigation, data curation, formal analysis, writing original draft and corresponding. Anisa Rohma Tika: Investigation, data curation, validation. Gita Nawangtantrini: Investigation, methodology, validation. Untung Gunarto: Supervision, methodology, writing and editing. Rizqi Yanuar Pauzi: Formal analysis, data interpretation, writing and editing. Muh. Asrun Putra Sahabuddin: Validation, data interpretation, writing and editing. All authors have read and approved the final version of the manuscript.