Journal of Applied Veterinary Science and Technology
http://e-journal.unair.ac.id/javest

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Research Reports

Nephroprotective Effect of Dayak Onion *(Eleutherine palmifolia)* Against Monosodium Glutamate-Induced Renal Toxicity in Mice *(Mus musculus)*

Efek Nefroprotektif Bawang Dayak *(Eleutherine palmifolia)* Terhadap Toksisitas Ginjal Akibat Monosodium Glutamat pada Mencit *(Mus musculus)*

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ABSTRACT

Background: The toxicological impacts of monosodium glutamate (MSG), a commonly used food additive, present a significant public health concern. Excessive MSG consumption will increase radical oxidative species, inducing a stress oxidative condition that ultimately results in kidney damage. **Purpose:** This study aimed to explore the nephroprotective effects of ethanol extracts from Dayak onion *(Eleutherine palmifolia)* against MSG-induced renal toxicity in mice *(Mus musculus)*. **Method:** Twenty-five 11 week-old male mice, weighing approximately 20 g each, were divided into five research groups. Group C- received only CMC-Na 0.5%, Group C+ received 4000 mg/kgBW MSG, while Groups T1, T2, and T3 were administered 4000 mg/kg BW MSG along with Dayak onion extract at doses of 30 mg/kg BW, 60 mg/kg BW, and 120 mg/kg BW respectively. All treatments were carried out orally for 52 days. The mice were euthanized by cervical dislocation, and their kidneys were extracted for the examination of any histopathological changes. The data underwent analysis utilizing the Kruskal-Wallis test, followed by the Mann-Whitney test. **Results:** The results as indicated by the histopathological evaluation of the mice's kidneys revealed significant improvements in the histo-architecture of the kidneys. Supplementation of Dayak onion extract in mice induced with MSG decreased the degeneration and necrosis of the tubule epithelium, and it also repaired the glomerular necrosis. **Conclusion:** Oral administration of Dayak onion extract to mice exposed to monosodium glutamate demonstrated a notable reduction in kidney damage and helped maintain renal health significantly.

ARTICLE INFO

Received: 23 Mei 2024
Revised: 24 July 2024
Accepted: 26 September 2024
Online: 31 October 2024

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Keywords: Dayak Onion; Monosodium Glutamate; Nephroprotective; Nephrotoxicity

ABSTRAK

Latar Belakang: Dampak toksikologi monosodium glutamat (MSG), bahan tambahan pangan yang umum digunakan, menimbulkan masalah kesehatan masyarakat yang signifikan. Konsumsi MSG yang berlebihan akan meningkatkan spesies oksidatif radikal yang akan menimbulkan kondisi stres oksidatif yang pada akhirnya mengakibatkan kerusakan ginjal. **Tujuan:** Penelitian ini bertujuan untuk mengeksplorasi efek nefroprotektif ekstrak etanol bawang Dayak *(Eleutherine palmifolia)* terhadap toksisitas ginjal yang diinduksi MSG pada tikus *(Mus musculus)*. **Metode:** Dua puluh lima tikus jantan berusia 11 minggu, dengan berat masing-masing sekitar 20 g, dibagi menjadi lima kelompok penelitian. Kelompok C- hanya menerima CMC-Na 0,5%, Kelompok C+ menerima MSG 4000 mg/kgBB, sedangkan Kelompok T1, T2, dan T3 diberikan MSG 4000 mg/kg BB bersama dengan ekstrak bawang Dayak pada dosis masing-masing 30 mg/kg BB, 60 mg/kg BB, dan 120 mg/kg BB. Semua perlakuan dilakukan secara oral selama 52 hari. Tikus dieutanasia dengan dislokasi serviks, dan ginjalnya diambil untuk pemeriksaan perubahan histopatologis. Data dianalisis menggunakan uji Kruskal-Wallis, diikuti dengan uji Mann-Whitney. **Hasil:** Hasil seperti yang ditunjukkan oleh evaluasi histopatologis ginjal tikus, menunjukkan perbaikan signifikan dalam histo-arsitektur ginjal. Suplementasi ekstrak bawang dayak pada tikus yang diinduksi dengan MSG mengurangi degenerasi dan nekrosis epitel tubulus, juga memperbaiki nekrosis glomerulus. **Kesimpulan:** Pemberian ekstrak bawang Dayak secara oral kepada tikus yang terpapar monosodium glutamat menunjukkan penurunan kerusakan ginjal yang signifikan dan membantu menjaga kesehatan ginjal secara signifikan.

Cite This Article:
Rahajeng, A.D.R., Rahmatullah, A.A., Putri, C.E.A., Sugihartuti, R., Suprihati, E., Plumeriastuti, H., Sukmanadi, M., and Hamid, I.S., 2024. ***Nephroprotective Effect of Dayak Onion (Eleutherine palmifolia) Against Monosodium Glutamate-Induced Renal Toxicity in Mice (Mus musculus).*** Journal of Applied Veterinary Science and Technology. 5(2):129-134. https://doi.org/10.20473/javest.V5.I2.2024.129-134

Kata kunci: Bawang Dayak; Monosodium Glutamate; Nephroprotektif; Nephrotoksik

INTRODUCTION

The use of traditional medicine is increasingly popular today as a means to address health issues. Dayak onion (*Eleutherine palmifolia*) is a wild plant native to the forests of Kalimantan (Kuntorini, 2013). It is commonly employed by inland communities as a traditional medicinal herb (Sumbayak and Vebriyani, 2019). Dayak onion contains a diverse array of phytochemical compounds, including alkaloids, glycosides, flavonoids, phenolics, steroids, and tannins, as well as secondary metabolites from the naphthoquinone group, such as elecanacin, ekeutherin, elutherol, and eleutherinon (da Silva *et al.,* 2024). These compounds have a potential for development into modern medicinal resources (Galingging, 2009). Research by Sharon *et al.,* (2013) has demonstrated that the flavonoid, phenolic, and tannin compounds in Dayak onions exhibit antioxidant activity. An ethanol extract of Dayak onion is shown to have a higher antioxidant capacity compared to ethanol extracts of shallots and garlic. This was evaluated using the DPPH (1,1-diphenyl-2-picrylhydrazyl) method, with IC50 values for the Dayak onion extract, garlic extract, and shallot extract measured at 25.33 ppm, 1915.393 ppm, and 1512.020 ppm, respectively (Kuntorini and Astuti, 2010; Soto, 2015). A lower IC50 value indicates greater free radical scavenging activity, with antioxidants considered to be very potent if their IC50 value is below 50 ppm (Mokoginta *et al.,* 2020).

The consumption of monosodium glutamate (MSG) in doses exceeding safety thresholds can lead to adverse effects on tissues and organs (Kayode *et al.,* 2020). Monosodium Glutamate contains free glutamate, which is unbound to protein molecules and can generate free radicals. The presence of free radicals in mice serves as an indicator of oxidative stress (Togatorop *et al.,* 2016). Farombi and Onyema (2006), found that the intraperitoneal administration of MSG at 4 mg/g body weight in rats induces oxidative stress, resulting in the production of Reactive Oxygen Species. Antioxidants, being natural compounds, play a crucial role in safeguarding lipid membranes against oxidation (Himawan *et al.,* 2021). The detrimental effects of free radicals within the body are counteracted by antioxidants (Togatorop *et al.,* 2016). The flavonoid compounds present in Dayak onions possess antioxidant properties, functioning as scavengers of free radicals by virtue of their hydroxyl groups, which act as reducers and donate hydrogen to free radicals (Sharon *et al.,* 2013). Moreover, the naphthoquinone-derived compounds found in Dayak onions are recognized for their bioactivity as both anticancer agents and antioxidants, existing in glycoside form within vacuolar cells (Kuntorini, 2013). Based on this explanation, this study was conducted to explore the nephroprotective effects of Dayak onion *(Eleutherine palmifolia)* extract and how it alters the histopathological appearance of the kidneys and counters MSG-induced renal toxicity in mice.

MATERIAL and METHOD

Experimental Design

The research employed a completely randomized design (CRD). A total of 25 male mice, aged 11 weeks and weighing 20 grams, were utilized for the study. Following a seven-day period of acclimatization for the experimental animals, a random sampling procedure was conducted to allocate each mouse to one of five treatment groups, with five mice assigned to each group. These treatment groups included: (C-) receiving rounded CMC Na 0.5%, (C+) administered 4 mg/g BB MSG, (T1) administered Dayak onion extract at a dosage of 30 mg/kgBW followed by MSG at 4 mg/g BW, (T2) administered Dayak onion extract at a dosage of 60 mg/kg BW followed by MSG at 4 mg/g BW, and (T3) administered Dayak onion extract at a dosage of 120 mg/kg BW followed by MSG at 4 mg/g BW. The Dayak onion extract was orally administered, followed by oral administration of MSG solution one hour later, from day 1 to day 52.

MSG and Dayak Onion Preparation

The MSG suspension was prepared by diluting MSG crystals in distilled water. The dosage utilized in this research was 4 mg/g BW (Sherbrina *et al.,* 2023). The Dayak onion extract *(Eleutherine palmifolia)* was derived from Dayak onion bulbs. These bulbs were thinly sliced and then sun-dried until completely dehydrated. Subsequently, the dried slices were ground into a powder. The Dayak onion powder underwent a maceration process in a 96% ethanol solution while being stirred until the ethanol solution was approximately 1 cm above the surface of the powder. The solution was then filtered using flannel cloth. The residue underwent repeated maceration until the obtained filtrate became clear. Extraction was conducted for 3x24 hours, with solvent replacement once daily. Following this, the filtrate was evaporated using a rotary evaporator at a temperature of 40°C at a speed of 40 rpm until it was no longer evaporating. The filtrate was then evaporated again using a water bath, and the weight of the resulting extract was measured (Ernawati and Nurliani, 2012). The Dayak onion extract was administered at doses of 30, 60, and 120 mg/kg WB orally, and each extract dose was dissolved in CMC-Na (Jayanti and Raudah, 2021).

Kidney Histopathological Sample Preparation

The basis for this study's treatment time period was derived from the previous research indicating the effectiveness of the selected duration in observing histopathological changes. Following the completion of treatments on day 53, all groups were euthanized by cervical dislocation (Flecknell, 2016). The abdominal wall was incised with scissors to extract the kidneys, which were subsequently preserved in a container containing 10% formalin. Histopathological alterations in the kidneys were examined using Hematoxylin-Eosin (HE) staining and microscopy at a magnification of 400x (Hamid *et al.,* 2022). The scoring method for assessing histopathological changes was based on the criteria outlined by Hamid *et al.,* (2022), where specific alterations were scored according to the severity and extent of damage observed under the microscope.

Data Analysis

The data underwent analysis utilizing the Kruskal-Wallis test, followed by the Mann-Whitney test if significant differences ($p<0.05$) were detected, in order to ascertain the variations within each group.

RESULTS

Prolonged excessive intake of MSG has been demonstrated to have nephrotoxic effects on the kidneys of mice (*Mus musculus*), manifested as the hydropic degeneration of the tubular epithelium, as well as tubular epithelium necrosis, and glomerular necrosis (Table 1 and Figure 1). The renal cortex is more prominently affected than the medulla, largely due to the fact that 90% of the total renal blood flow is directed to the cortex, resulting in higher concentrations of MSG reaching the cortex compared to the medulla (Jarrar *et al.*, 2013). The underlying mechanism of tubular and glomerular damage is believed to stem from the excessive activation of glutamate receptors on the cellular structures. Elevated plasma glutamate levels lead to the free filtration of amino acids by the glomerulus, resulting in filtration outcomes equivalent to plasma concentration. The filtrated glutamate activates the ionotropic and metabotropic glutamate receptors in the tubular cells, including the NMDA receptors. This activation subsequently triggers an increase in cytoplasmic calcium ion levels, disrupting the Na-K ATPase channel and resulting in cellular edema due to water accumulation in the cytoplasm (Hussin *et al.*, 2021).

Tabel 1. Hydropic Degeneration, Tubular Epithelial Necrosis, and Glomerular Necrosis in the Mice Kidneys

Treatment	Degeneration (Mean ± SD)	Necrosis (Mean ± SD)	Glomerular Necrosis (Mean ± SD)
C-	$1{,}72^{a} \pm 0.303$	$2{,}64^{a} \pm 0{,}456$	$3{,}96^{a} \pm 0{,}669$
C+	$3{,}44^{b} \pm 0{,}167$	$6{,}32^{b} \pm 0{,}955$	$8{,}20^{b} \pm 1{,}131$
T1	$2{,}56^{c} \pm 0{,}498$	$4{,}64^{c} \pm 0{,}669$	$5{,}88^{c} \pm 0{,}769$
T2	$2{,}00^{ac} \pm 0{,}400$	$3{,}20^{d} \pm 0{,}282$	$4{,}20^{a} \pm 0{,}282$
T3	$1{,}40^{a} \pm 0{,}316$	$2{,}32^{a} \pm 0{,}438$	$3{,}24^{a} \pm 0{,}358$

Note: Different superscripts in the same column show the significant differences ($p < 0.05$).

DISCUSSION

Hydropic Degeneration

Hydropic degeneration refers to the swelling of cells due to excessive water accumulation in the cytoplasm, which leads to cellular enlargement (Maremonti *et al.*, 2022). This occurrence arises when cells fail to maintain their ion and fluid balance. Hydropic degeneration commonly manifests as acute cell swelling due to a water influx diluting the cytosol, separating the organelles, and distorting the rest of the cell morphology, resulting in swollen, pale, and finely vacuolated cells (Miller and Zachary, 2017). In this investigation, Group C+ exhibited the highest degree of hydropic degeneration in the tubule epithelium. This was induced by administering MSG at 4 mg/g BW over a span of 52 days. MSG leads to hydropic degeneration primarily through oxidative stress. MSG contains glutamic acid, which increases ROS by over-activating the glutamate receptors, leading to mitochondrial dysfunction and cell swelling (Abd-Elkareem *et al.*, 2022). Dayak onion extract counteracts this by providing antioxidants that neutralize free radicals and reduce cellular damage. This imbalance triggers an increase in Reactive Oxygen Species (ROS), resulting in DNA and RNA damage, as well as heightened protein and lipid peroxidation (Tirichen *et al.*, 2021). These damages lead to cellular-level issues such as mitochondrial dysfunction. Mitochondria serve as sites for Adenosine Triphosphate (ATP) synthesis. Consequently, mitochondrial damage diminishes the ATP production required by the body, ultimately inducing programmed cell death or apoptosis in the renal tubule cells, resulting in cell injury (Zhang *et al.*, 2021). Cell injury prompts an influx of extracellular fluid into the cell, causing a loosening of the constituent epithelium of the proximal tubules and facilitating the entry of various components into the tubule cells. This shift culminates in the swelling of the proximal cortical tubule epithelial cells or hydropic degeneration (Rao *et al.*, 2023).

The findings of this study indicate that Groups T1, T2, and T3 experienced lower levels of hydropic degeneration compared to Group C+, which solely received MSG at 4 mg/g BW. This is attributed to the administration of the Dayak onion ethanol extract as an antioxidant prior to exposure, which exerts a protective effect on the cells, thereby reducing cellular damage. The degree of hydropic degeneration decreases with an increase in the Dayak onion dose. This suggests that compounds such as polyphenols and flavonoids present in the ethanol extract of Dayak onion possess the ability to scavenge free radicals by providing hydrogen ions (Annisa *et al.*, 2021). The components of Dayak onions that are potent antioxidants are phenolics, flavonoids, and tannins (Yuanita *et al.*, 2020). Polyphenolic compounds, such as flavonoids and phenols, are able to inhibit antioxidants through a radical capture mechanism by donating one electron to an unpaired electron in a free radical, so then the number of free radicals is reduced. Phenol compounds include a wide variety of compounds derived from plants which have the same characteristics, namely aromatic rings containing one or two hydroxyl groups. Flavonoids are good reducing compounds, inhibiting many oxidation reactions both enzymatically and non-enzymatically. Flavonoids act as good reservoirs for hydroxyl and superoxide radicals, thereby protecting membrane lipids against damaging reactions. The hydroxyl groups present in phenol compounds provide their electrons so as to counteract free radicals from the peroxidation chain (Rudrapal *et al.*, 2022).

Tubular Epithelial Necrosis

Tubular epithelial necrosis results from severe and irreversible cell injury due to toxins, hypoxia, or ischemia. Necrosis is marked by nuclear changes such as pycnosis (nucleus shrinkage), karyorrhexis (nucleus fragmentation), and karyolysis (nucleus dissolution) (Maremonti *et al.*, 2022). The microscopic changes associated with necrosis are characterized by the presence of pycnosis, karyorrhexis, and karyolysis. Pycnosis manifests as nucleus condensation with shrinkage and increased basophilia, karyorrhexis is marked by nucleus fragmentation, and karyolysis is distinguished by pale, swollen, rounded nuclei detached from the neighboring cells' basement membrane. Kidney damage in the form of tubular necrosis can be attributed to various toxic substances since the tubular epithelial cells are directly exposed to reabsorbed material, making them susceptible to damage or necrosis in the cell nucleus (Rao *et al.*, 2023). This may result from elevated levels in the bloodstream, triggering the NMDA

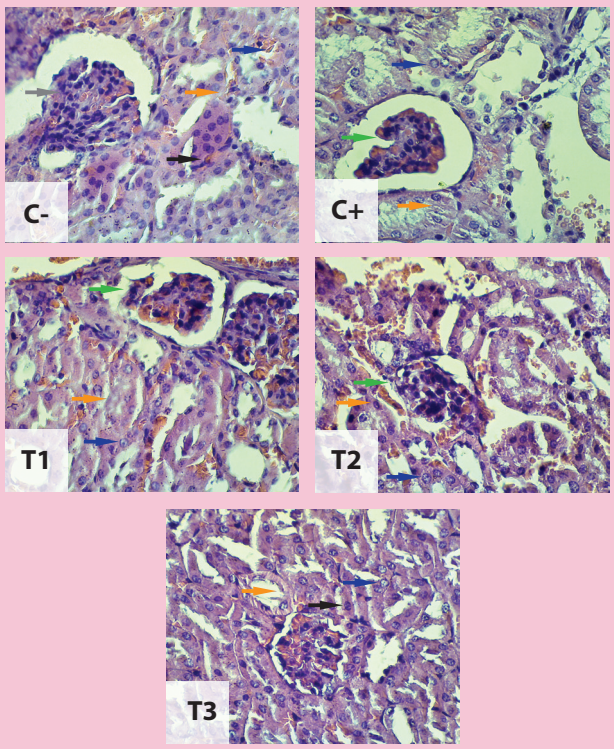

Figure 1. Histopathological features of the kidney in mice using HE staining at 400x magnification. Hydropic degeneration on the tubular epithelial (blue arrow), tubular epithelial necrosis (orange arrow), glomerular necrosis (green arrow), normal tubular cells (black arrow), and normal glomerulus (gray arrow).

neurotransmitter receptors and subsequently opening calcium ion channels. Consequently, there is an influx of calcium ions and the generation of free oxygen radicals. MSG-induced necrosis involves a calcium ion influx and ROS generation, leading to lipid peroxidation and cell membrane rupture (Yogiana *et al.*, 2021). This study found that the tubular necrosis was significantly lower in Groups T1, T2, and T3 compared to Group C+. The protective effects were dose-dependent, with the best results at 120 mg/kg BW.

Glomerular Necrosis

Glomerular necrosis is characterized by significant atrophy or shrinkage of the glomerular cells and the presence of empty spaces within the cells resulting from lysing activity by phagocytic cells (Rao *et al.*, 2023). Glomerular necrosis involves the atrophy and death of glomerular cells, leading to decreased glomerular filtration and the accumulation of toxins (Nurcahyawati, 2017). The functional impairment of the glomerulus is marked by decreased blood flow perfusion and the leakage of proteins and other macromolecules in large quantities into the glomerular filtrate. This results in reduced blood flow, protein leakage, and atrophy of the renal tubules (Sastyarina, 2012). According to the study findings, the C+ group exhibited the highest incidence of glomerular necrosis, likely due to the exclusive administration of MSG at a dosage of 4 mg/kg BW. Conversely, as the preventive dose of Dayak onion ethanol extract increased, the incidence of glomerular necrosis significantly decreased in the treatment groups.

The compounds present in Dayak onions, including alkaloids, glycosides, phenolics, steroids, flavonoids, and tannins, function as antioxidants capable of inhibiting the formation and activity of free radicals, preventing severe cellular damage. Dayak onion extract contains polyphenols and flavonoids, which are potent antioxidants. These compounds neutralize free radicals by donating hydrogen atoms or electrons, thus stabilizing the radicals and reducing oxidative stress. Flavonoids and phenols prevent oxidation by providing electrons to free radicals, which protects the cell membranes and reduces damage (Annisa *et al.*, 2021). The presence of flavonoids and tannins serve as antioxidants that mitigate kidney pathology, with higher concentrations of these active compounds correlating with reduced levels of epithelial and glomerular necrosis (Nurcahyawati *et al.*, 2017). Groups T2 and T3 demonstrated effective preventive doses in averting glomerular necrosis, as evidenced by their non-significant differences from the C+ group. These findings suggest that the administration of Dayak onion ethanol extract, with a minimum preventive dose of 60 mg/kg BW in mice (*Mus musculus*) exposed to MSG, exerts a protective effect on the histopathological structure of the kidneys. In this study, 120 mg/kg BW is deemed to be the optimal dose.

CONCLUSION

The administration of Dayak onion extract (*Eleutherine palmifolia*) acts as a nephroprotective agent against monosodium glutamate-induced renal toxicity in mice (*Mus musculus*). The extract improves the histopathological appearance of the kidneys by significantly reducing the severity of lesions, including hydropic degeneration, tubule epithelial necrosis, and glomerular necrosis, with the optimal protective effect observed at a dosage of 120 mg/kg BW.

ACKNOWLEDGEMENT

The author would like to express their appreciation of the faculty members and staff of the Faculty of Veterinary Medicine, Airlangga University for their valuable support and contributions to this research.

CONFLICT of INTEREST

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

RESEARCH FUNDING

This research is self-funded.

ETHICAL APPROVAL

This experiment was performed based on approval for the laboratory animals use by the Research Ethics Committee of the Faculty of Veterinary Medicine [1.KEH.081.07.2022], Airlangga University, Indonesia

AUTHORS' CONTRIBUTIONS

ADRR and CEAP: Drafted the manuscript. AAR: Conceptualization of the research and conducted the statistical analysis. AAR and ADRR: Handled the animal experiments in the

laboratory and did the histopathological examination. RS, ES, HP, MS and ISH: Validation, supervision, and formal analysis. All authors have read, reviewed, and approved the final manuscript.

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