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Original Research

Ameliorative Effects of Eleutherine palmifolia Extract on Monosodium Glutamate-Induced Reproductive Toxicity: Modulation of Oxidative Stress Markers and Spermatogenesis in a Murine Model

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Abstract

Chronic monosodium glutamate (MSG) exposure is linked to testicular toxicity, impacting spermatogenesis and oxidative stress markers. This study investigated the protective effects of Dayak onion (Eleutherine palmifolia) extract against MSG-induced testicular damage in mice. Twenty-five male mice (11 weeks, ~20 g) were divided into five groups: negative control (C-, 0.5% CMC-Na), positive control (C+, MSG 4 mg/g BW), and treatment groups (T1, T2, T3) receiving MSG plus Dayak onion extract (30, 60, 120 mg/kg BW, respectively) for 52 days. On day 53, testicular histology and serum malondialdehyde (MDA) and superoxide dismutase (SOD) levels were analyzed. One-way ANOVA and Duncan's post hoc test assessed differences ($p<0.05$). Group C+ showed significantly reduced spermatogenic cell counts, elevated MDA, and decreased SOD compared to C-. Group T1 exhibited no significant improvement in spermatogonia and spermatocytes but increased spermatids. Groups T2 and T3 significantly improved spermatogenic cell counts, with T3 showing the closest recovery to C-. MDA levels decreased, and SOD activity increased dose-dependently, with T3 nearing C- levels. Dayak onion extract, particularly at 120 mg/kg BW, mitigates MSG-induced testicular toxicity, preserving spermatogenesis and balancing oxidative stress markers

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1. Introduction

Monosodium glutamate (MSG) is a widely used food additive that has been associated with various health concerns, including testicular toxicity. Chronic exposure to MSG has been shown to negatively impact male reproductive health by disrupting spermatogenesis and increasing oxidative stress in testicular tissue.[1] This disruption occurs as excess glutamate from MSG triggers significant oxidative stress in testicular cells, leading to the overproduction of reactive oxygen species (ROS) in the mitochondria.[2] The resulting lipid peroxidation damages cell membranes and intracellular organelles, producing elevated levels of malondialdehyde (MDA), an important marker of oxidative damage.[3]

The oxidative stress caused by MSG exposure has multifaceted effects on testicular health. It reduces the activity of natural antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), further intensifying the oxidative damage to testicular cells.[4] Additionally, continued oxidative stress can trigger apoptosis in germ cells through the activation of the intrinsic apoptosis pathway involving cytochrome c release and caspase activation.[5] MSG also disrupts the hypothalamic-pituitary-gonadal axis, affecting the secretion of crucial hormones including Gonadotropin-Releasing Hormone (GnRH), Luteinizing Hormone (LH), and Follicle-Stimulating Hormone (FSH), which collectively impairs testosterone production by Leydig cells and compromises normal spermatogenesis.[6]

Antioxidants play a vital role in preventing diseases caused by free radicals and neutralizing excess reactive oxygen species that lead to oxidative stress.[7-8] Among the endogenous antioxidant defense systems, SOD serves as the first line of defense against ROS, catalyzing the dismutation of superoxide radicals into hydrogen peroxide, which is subsequently detoxified by catalase and glutathione peroxidase.[9] In testicular tissue specifically, SOD activity is crucial for maintaining the integrity of spermatogenic cells and protecting against oxidative damage during the sensitive process of spermatogenesis.[7] The balance between oxidative stress and antioxidant defense mechanisms is therefore essential for preserving normal testicular function and fertility.

The Dayak onion (Eleutherine palmifolia) presents a promising natural remedy for MSG-induced testicular toxicity due to its rich content of bioactive compounds. This plant has been traditionally used by the Dayak community for various medicinal purposes, including treating cancer, hypertension, diabetes mellitus, and wounds.[10] The therapeutic potential of Dayak onion stems from its abundant secondary metabolites, particularly in the bulbs, which contain flavonoids, phenolics, and napthoquinone compounds such as elecanacine, eleutherine, iso-eleutherine, eleutherol, and eleuthernone.[9] The leaves also contain beneficial compounds including flavonoids, saponins, phenols, and tannins.[11] These plant compounds, especially flavonoids and phenolics, exhibit significant antioxidant properties that may help counteract the oxidative damage caused by MSG exposure.[12] This research therefore aims to investigate the protective potential of Dayak onion extract against testicular toxicity induced by chronic MSG exposure in mice.

2. Method

Preparation of MSG and Dayak Onion Extract

Monosodium glutamate (MSG) suspension was prepared by dissolving MSG crystals in distilled water to achieve a dose of 4 mg/g body weight (BW).[13] Dayak onion (Eleutherine palmifolia) bulbs were collected from South Kalimantan, Indonesia. The bulbs were thinly sliced, sun-dried, and pulverized into a fine powder. The powder was subjected to maceration in 96% ethanol, with the solvent level maintained approximately 1 cm above the powder surface, and stirred periodically. The mixture was filtered using flannel cloth, and the residue was re-macerated until the filtrate appeared clear. Maceration was conducted over three 24-hour cycles, with daily solvent replacement. The filtrate was concentrated using a rotary evaporator at 40°C and 40 rpm until no further evaporation occurred, followed by additional evaporation in a water bath. The extract was dissolved in 0.5% carboxymethylcellulose sodium (CMC-Na) and administered orally at 30, 60, and 120 mg/kg BW, selected based on previous studies demonstrating antioxidant efficacy of E. palmifolia at these doses without toxicity in mice.[14]

Animal Treatment and Experimental Design

Twenty-five male mice (11 weeks old, about 20 g each) were used in this study, following a completely randomized design (CRD) with five treatment groups, each replicated five times. Group C- received 0.5% CMC-Na orally (negative control), while Group C+ was administered MSG at 4 mg/g BW orally (positive control). Groups T1, T2, and T3 received MSG at 4 mg/g BW followed by Dayak onion extract at 30, 60, and 120 mg/kg BW, respectively, administered orally one hour after MSG. The mice underwent a 7-day

acclimatization period, followed by a 52-day treatment phase.

On day 53, the mice were anesthetized via atlanto-occipital cervical dislocation, followed by organ harvesting. Testes were collected and preserved in 10% formalin for histopathological examination using hematoxylin and eosin staining. Histopathological examination was performed using a Nikon Eclipse microscope at 400x magnification to determine the number of spermatogenic cells. Spermatogenic cell counts were averaged from five visual fields.[15] Intracardiac blood was collected for measuring MDA levels and SOD enzym activity. MDA levels and SOD enzyme activity were measured in serum samples using the ELISA colorimetric method. MDA levels reported in units of μmol/L meanwhile SOD enzym acitivity reported in units of U/mL.[16]

Statistical Analysis

Data analysis was performed using the Statistical Product and Service Solution (SPSS) software. A one-way analysis of variance (ANOVA) was employed to determine differences among treatment groups. If there was a significant difference among the research groups ($p<0.05$), a Duncan's post hoc test was conducted.

3. Result

The mean count of spermatogenic cells was determined from histopathological samples using the Nikon Eclipse E-100 microscope, and calculations were conducted using image analysis software at a magnification of 400x across five fields of view. MDA and SOD levels were assessed via a colorimetric method employing a spectrophotometer set at an absorbance of 450 nm, and results were compared against a standard curve. Overall, the findings indicated a statistically significant distinction ($p < 0.05$) in both spermatogenic cell counts MDA and SOD serum levels between the control group and the various treatment groups (Table 1, Table 2, Figure2, Figure 3 and Figure 4).

Table 1. The average results of the number of spermatogenic cells in male mice given *Eleutherine palmifolia* extract and exposed to monosodium glutamate**.**

Treatments	Mean ± SD		
	Spermatogonia	Spermatosit	Spermatid
C-	$33.72^{c} \pm 1.15$	$49.80^{b} \pm 2.70$	$89.24^{c} \pm 3.51$
C+	$20.40^{a} \pm 0.92$	$29.72^{a} \pm 3.04$	$56.20^{a} \pm 8.28$
T1	$21.48^{a} \pm 1.15$	$30.44^{a} \pm 4.32$	$79.08^{b} \pm 6.91$
T2	$28.12^{b} \pm 1.06$	$45.64^{b} \pm 3.52$	$84.28^{bc} \pm 4.00$
T3	$30.48^{c} \pm 1.11$	$49.92^{b} \pm 2.40$	$88.64^{c} \pm 4.41$

Note: Different superscripts (a,b,c,d,e) indicate significant differences between groups ($p<0,05$) by Duncan's post hoc test.

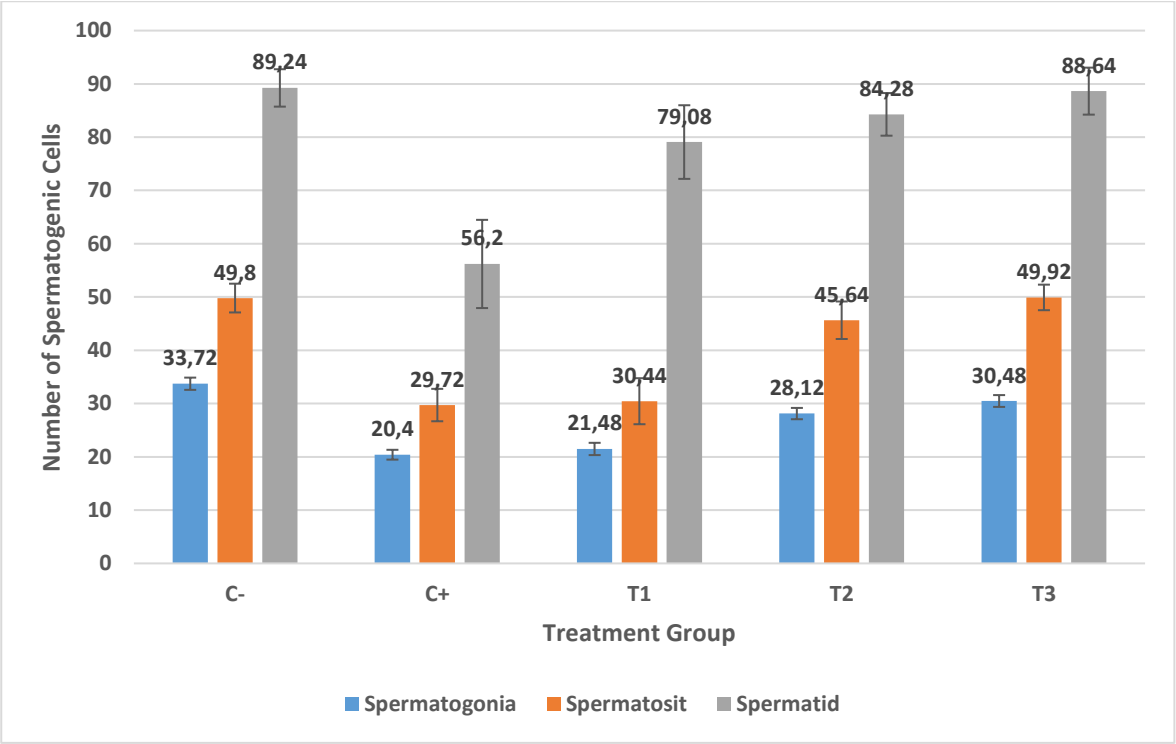
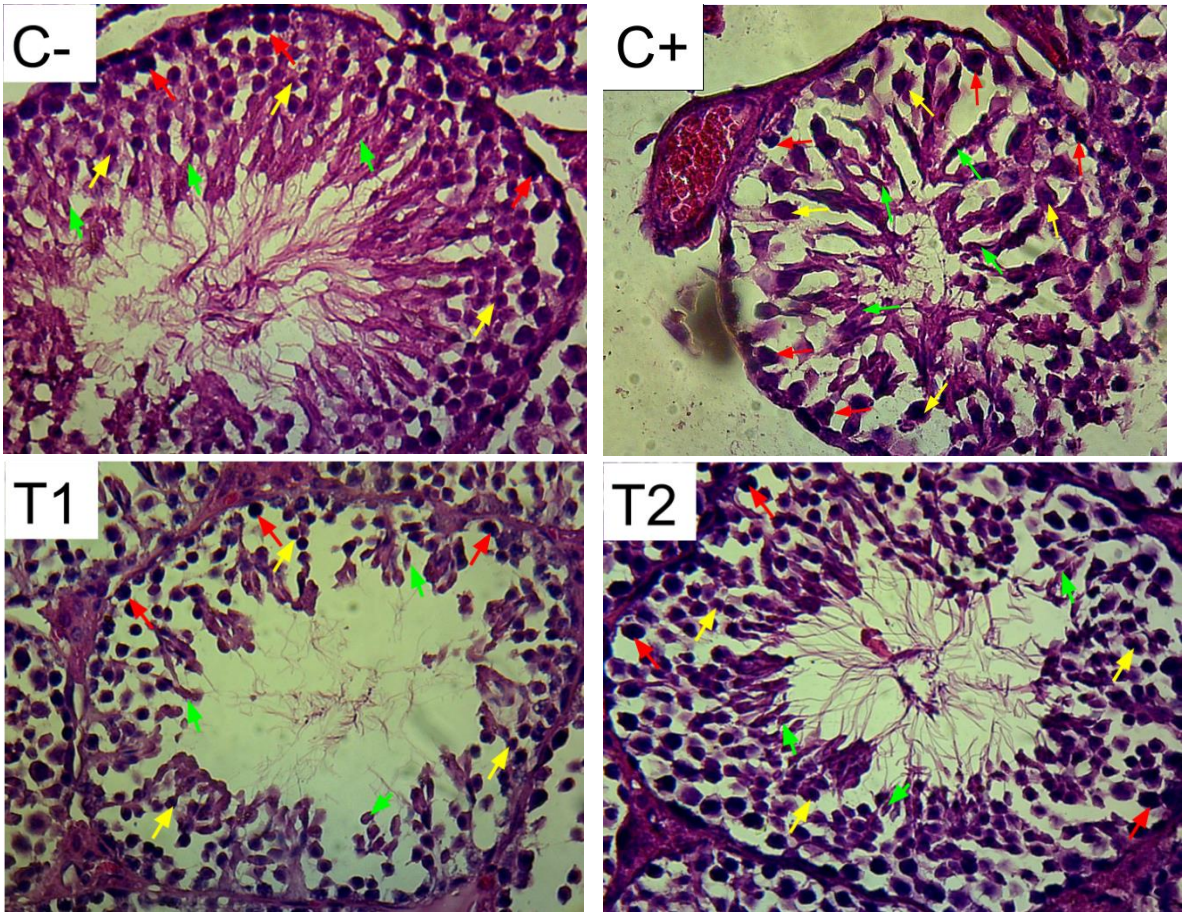


Figure 1. Comparison diagram of spermatogenic cell examination results after exposed to monosodium glutamate (MSG) treated with *Eleutherine palmifolia* extract.



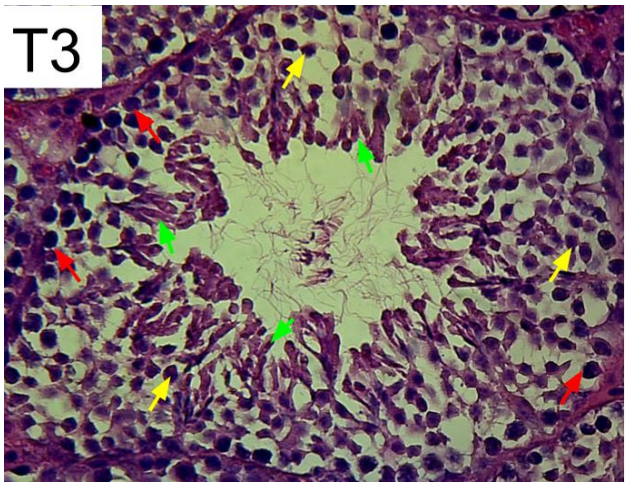


Figure 2. Histopathological Preparation of Mouse Seminiferous Tubules with HE Staining at 400x Magnification (Red Arrow = Spermatogonia, Yellow Arrow = Spermatocytes, Green Arrow = Spermatids).

Table 2. The average results of the MDA and SOD serum level in male mice given *Eleutherine palmifolia* extract and exposed to monosodium glutamate.

Treatments	MDA Level (µmol/L) (Mean ± SD)	SOD Level (U/mL) (Mean ± SD)
C-	$10.92^{d} \pm 3.07$	$195.42^{c} \pm 22.43$
C+	$36.94^{a} \pm 4.50$	$131.97^{a} \pm 20.87$
T1	$23.63^{b} \pm 5.73$	$148.54^{ab} \pm 16.37$
T2	$17.08^{c} \pm 2.64$	$154.52^{ab} \pm 15.95$
T3	$13.30^{cd} \pm 1.64$	$179.65^{bc} \pm 21.22$

Note: Different superscripts (a,b,c,d,e) indicate significant differences between groups ($p<0,05$) by Duncan's post hoc test

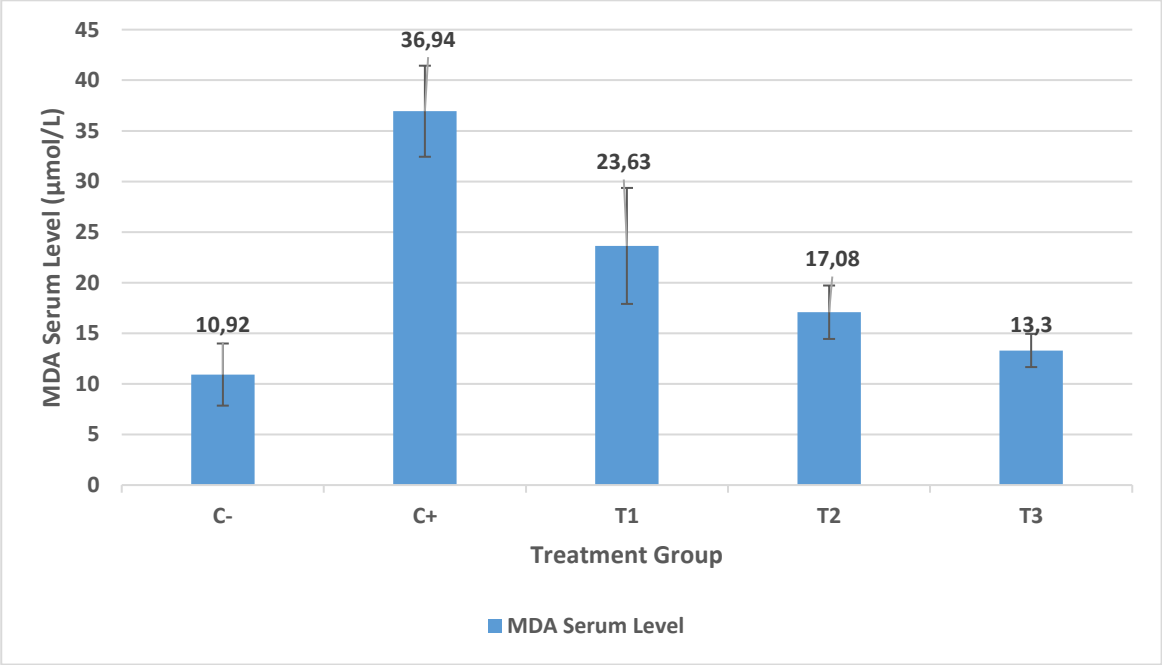


Figure 3. Comparison diagram of MDA serum level after exposed to monosodium glutamate (MSG) treated with *Eleutherine palmifolia* extract.

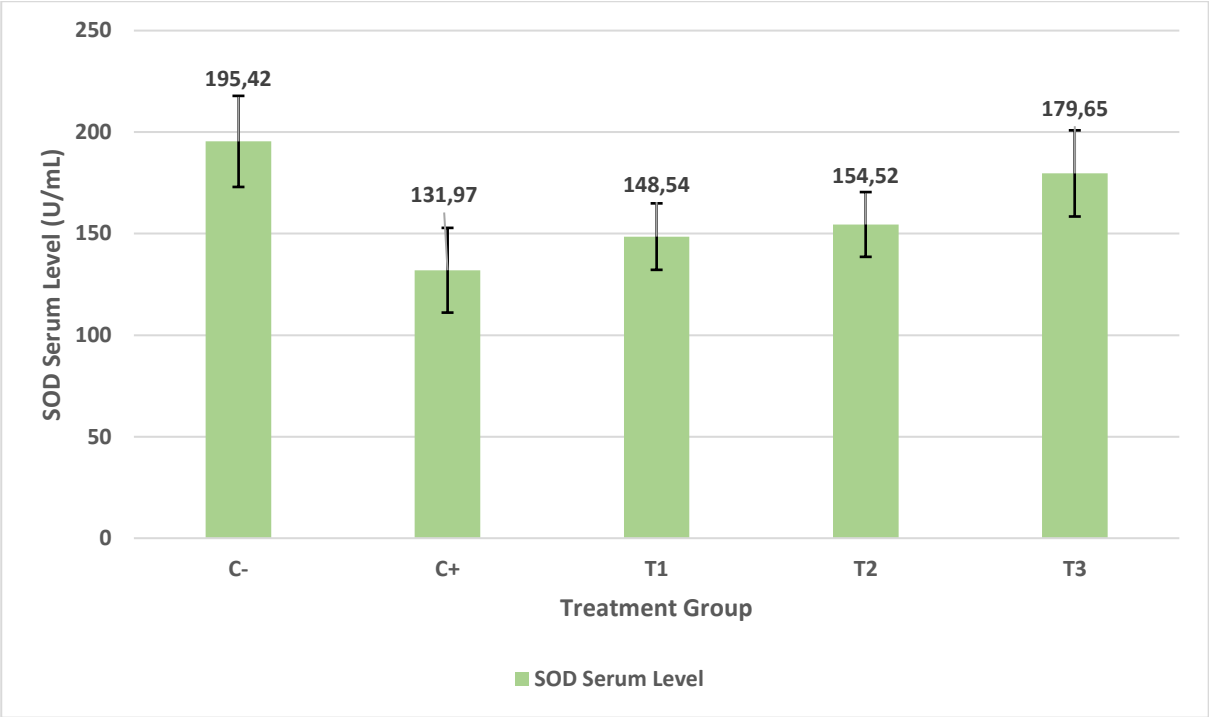


Figure 4. Comparison diagram of SOD serum level after exposed to monosodium glutamate (MSG) treated with *Eleutherine palmifolia* extract.

The evaluation of spermatogenic cells in male mice revealed significant differences between the control and treatment groups ($p < 0.05$). The negative control group (C-) exhibited the highest mean spermatogonia count (33.72 ± 1.15), while the positive control group (C+) exposed to monosodium glutamate without treatment showed a marked reduction (20.40 ± 0.92), indicating MSG's detrimental impact on testicular cells. The administration of *Eleutherine palmifolia* extract demonstrated a dose-dependent protective effect, with the T3 group (120 mg/kg BW) showing the most substantial recovery of spermatogonia counts (30.48 ± 1.11), approaching levels similar to the negative control. Histopathological examination of mouse seminiferous tubules with HE staining at 400x magnification clearly visualized the different cell types involved in spermatogenesis, confirming the quantitative findings of the cellular analysis.

Similar trends were observed in spermatocyte and spermatid counts across the experimental groups. The MSG-exposed positive control group (C+) showed significantly reduced spermatocyte (29.72 ± 3.04) and spermatid (56.20 ± 8.28) counts compared to the negative control group (49.80 ± 2.70 and 89.24 ± 3.51, respectively). The T1 group (30 mg/kg BW of extract) showed no significant improvement in spermatocyte counts (30.44 ± 4.32) compared to C+, but demonstrated a significant increase in spermatid counts (79.08 ± 6.91). The T2 group (60 mg/kg BW) exhibited significant improvements in both spermatocyte (45.64 ± 3.52) and spermatid (84.28 ± 4.00) counts, while the T3 group (120 mg/kg BW) showed the most substantial recovery, with values (49.92 ± 2.40 for spermatocytes and 88.64 ± 4.41 for spermatids) closely approximating those of the negative control group. These findings suggest that *Eleutherine palmifolia* extract at higher doses effectively preserves spermatogenesis against MSG-induced damage.

The assessment of oxidative stress markers further supported the protective effects of *Eleutherine palmifolia* extract. Serum malondialdehyde (MDA) levels, an indicator of lipid peroxidation, were significantly elevated in the MSG-exposed positive control group (36.94 ± 4.50 µmol/L) compared to the negative control (10.92 ± 3.07 µmol/L). The treatment groups showed a dose-dependent reduction in MDA levels, with the T3 group (13.30 ± 1.64 µmol/L) approaching levels similar to the negative control. Conversely, superoxide dismutase (SOD) activity, a critical antioxidant enzyme, was significantly reduced in the positive control group (131.97 ± 20.87 U/mL) compared to the negative control (195.42 ± 22.43 U/mL). The extract treatment groups showed a dose-dependent recovery of SOD activity, with the T3 group (179.65 ± 21.22 U/mL) demonstrating SOD levels most comparable to the negative control. These findings collectively indicate that *Eleutherine palmifolia* extract mitigates MSG-induced oxidative stress in

testicular tissue, with the highest dose (120 mg/kg BW) providing the most effective protection.

4. Discussions

The excessive exposure of mice to monosodium glutamate (MSG) triggers a series of destructive biochemical reactions, beginning with a drastic increase in glutamate levels in the body.[17] This excess glutamate enters cells through specific transporters such as Excitatory Amino Acid Transporters (EAAT), initiating a cascade of reactions leading to intense oxidative stress.[18] Inside the cell, particularly in mitochondria, excess glutamate stimulates massive production of reactive oxygen species (ROS).[19] This occurs because glutamate accelerates the activity of the electron transport chain, generating more superoxide (O2-) as a byproduct.[20] Additionally, glutamate also activates the NADPH oxidase (NOX) enzyme in cell membranes, further increasing ROS formation. As a result, the cell's redox balance is disrupted, creating a highly oxidative environment.[21]

This oxidative environment severely compromises the activity of superoxide dismutase (SOD), a critical first-line antioxidant enzyme. SOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, which is then neutralized by catalase and glutathione peroxidase.[7] Under normal conditions, SOD maintains redox homeostasis in testicular tissue, protecting developing spermatogenic cells from oxidative damage. However, with MSG exposure, SOD activity becomes significantly depleted as the enzyme is overwhelmed by excessive superoxide production.[19] This depletion of SOD activity serves as a reliable marker of oxidative stress and correlates with the degree of testicular damage and reduced spermatogenesis observed in MSG-exposed animals.[16]

These excessive ROS then attack various cellular components, especially membrane lipids rich in polyunsaturated fatty acids. This process, known as lipid peroxidation, produces various products including malondialdehyde (MDA).[22] The formed MDA then leaks from damaged cells into the bloodstream, causing a significant increase in serum MDA levels.[23]

Simultaneously, this oxidative stress has a damaging impact on spermatogenic cells in the testes. ROS damage DNA, cell membranes, and proteins in these cells, disrupting their normal function.[24] DNA damage inhibits the expression of key genes necessary for spermatogenesis, while membrane damage interferes with the function of receptors and ion channels crucial for proper sperm cell development.[25] Furthermore, oxidative stress activates the intrinsic apoptosis pathway in spermatogenic cells.[26] ROS trigger the release of cytochrome c from mitochondria to the cytosol, which then activates caspase-9 and caspase-3, leading to programmed cell death. This process directly reduces the number of living spermatogenic cells.[27]

At the systemic level, excess glutamate also disrupts the balance of reproductive hormones by affecting the hypothalamic-pituitary-testicular (HPT) axis.[28] This disruption results in decreased testosterone production by Leydig cells and impaired function of Sertoli cells, both of which are essential for normal spermatogenesis.[29] The combination of direct cell damage and hormonal disturbances results in a significant decrease in the number of spermatogenic cells in the seminiferous tubules of the testes.

Amidst the damage caused by MSG, Dayak Onion extract (*Eleutherine palmifolia*) emerges as a potential protective agent. Rich in bioactive compounds such as flavonoids, phenols, and naphthoquinones this extract works through various mechanisms to counteract the damaging effects of MSG.[9] At the molecular level, antioxidant compounds such flavonoids and phenolics in dayak onion act as effective free radical scavengers. They neutralize ROS before they can damage cellular components, effectively reducing the level of oxidative stress. Additionally, this extract also inhibits pro-oxidant enzymes and binds metal ions involved in free radical formation, further reducing the oxidative burden on cells.[30]

Equally important, dayak onion extract enhances the body's antioxidant defense system by stimulating the production of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The bioactive compounds in Dayak onion extract particularly restore SOD activity in testicular tissue. Flavonoids and phenolic compounds activate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that upregulates antioxidant genes, including SOD, by binding to antioxidant response elements (ARE). Flavonoids stabilize Nrf2 by inhibiting its degradation, enhancing SOD expression.[9] The restoration of SOD activity is crucial for neutralizing superoxide radicals at their source, preventing the initiation of oxidative damage cascades in spermatogenic cells.[8] Increased activity of these enzymes helps cells cope with oxidative stress more effectively.[31]

In spermatogenic cells, compounds in dayak onion extract help maintain cell membrane integrity, protect DNA from oxidative damage, and

inhibit stress-induced apoptosis pathways.[32] This extract also supports optimal mitochondrial function, which is crucial for energy production during spermatogenesis.[33]

Furthermore, bioactive compounds such as flavonoids, phenols and naphthoquinones can modulate signaling pathways involved in the proliferation and differentiation of spermatogenic cells, such as the phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways.[34] This modulation helps maintain the survival and normal function of spermatogenic cells amidst MSG exposure. At the systemic level, dayak onion extract helps maintain reproductive hormone balance by supporting HPT axis function. By protecting Leydig and Sertoli cells from oxidative damage, this extract helps maintain adequate testosterone production and an optimal microenvironment for sperm cell development.[35]

Through these multi-level actions, dayak onion extract effectively reduces MDA formation, lowers serum MDA levels, while maintaining the quantity and quality of spermatogenic cells in MSG-exposed mice. The result is comprehensive protection of male reproductive function from the adverse effects of MSG-induced oxidative stress. The therapeutic potential of dayak onion extract paves the way for the development of natural strategies to protect male reproductive health from MSG exposure and similar substances that can trigger oxidative stress. With its ability to reduce serum MDA levels and maintain spermatogenic cell numbers, dayak onion extract offers a promising approach to addressing oxidative stress-related infertility issues, particularly those caused by excessive MSG exposure.

5. Conclusion

This study demonstrates that Dayak onion (*Eleutherine palmifolia*) extract effectively mitigates monosodium glutamate (MSG)-induced testicular toxicity in male mice by modulating oxidative stress markers and preserving spermatogenesis. Chronic MSG exposure significantly impaired testicular function, reducing spermatogenic cell counts, elevating malondialdehyde (MDA) levels, and decreasing superoxide dismutase (SOD) activity. However, *E. palmifolia* extract provided dose-dependent protection, with the highest dose (120 mg/kg BW) yielding therapeutic benefits closest to the negative control group. The extract's antioxidant properties, driven by flavonoids, phenolics, and naphthoquinones, scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, and enhance endogenous antioxidant defenses, thereby maintaining testicular cellular integrity and supporting normal spermatogenesis.

Despite these findings, the absence of hormonal data (testosterone, LH, FSH) limits insights into the extract's effects on the hypothalamic-pituitary-testicular axis, a critical factor in MSG-induced reproductive toxicity. Future research should quantify specific bioactive compounds, investigate inflammatory pathways, and measure hormonal markers to elucidate systemic mechanisms. These studies will strengthen the translational potential of *E. palmifolia* extract as a nutraceutical for mitigating oxidative stress-related male infertility caused by dietary toxicants like MSG.

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Authors' Contributions

All authors have contributed to the final manuscript

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Clearance

This study was ethically approved with clearance number 1.KEH.081.07.2022 from the Animal Care and Use Committee at the Faculty of Veterinary Medicine, Universitas Airlangga

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