

Research Article

6-Gingerol Reduces Tumor Necrosis Factor-Alpha Levels in the Brain of Metabolic Syndrome Rats

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Abstract

Metabolic syndrome (MetS), with its associated abnormalities, is linked with oxidative stress and inflammation in the brain, leading to cognitive decline. As a natural compound with promising antioxidant properties derived from ginger, 6-gingerol (6G) could be a potential therapeutic candidate. This study aimed to investigate the effects of 6G on alleviating inflammation, oxidative stress, and insulin signaling in the brain tissue of MetS rats. Male Sprague-Dawley Rats were randomized into five groups: normal control, negative control, and three groups receiving increasing doses of 6G for 8 weeks. A high-fat diet and a low-dose streptozotocin injection induced MetS. Brain tissues were analyzed for tumor necrosis factor (TNF- α), interleukin-1 (IL-1 β), malondialdehyde (MDA), glutathione peroxidase (GPx), glucagon-like peptide (GLP-1), and GLP-1 receptor (GLP-1R) levels. The study was conducted at the Pharmacokinetics Laboratory Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, in January-February, 2023. TNF- α levels were significantly higher in the MetS group compared to the normal-control group (95% CI: -4.4 – -74.9; $p = 0.024$), whereas there were no significant differences in IL-1 β , MDA, GPx, GLP-1, and GLP-1R levels between the MetS and normal-control groups. Administration of 6G at 50 mg/kg/day significantly reduced TNF levels compared with the MetS group (95% CI: -12 to -82; $p = 0.006$), whereas 6G at 100 and 200 mg/kg/day did not improve all parameters. The present findings suggest that 6G, particularly at a dose of 50 mg/kg, may exert anti-inflammatory effects in MetS-induced brain inflammation. However, the importance of dose optimization for the potential translational application of 6G remains to be further researched.

Keywords: 6-gingerol, antidiabetics, antioxidants, brain, metabolic syndrome.

6-gingerol Menurunkan Kadar Tumor Nekrosis Faktor-Alfa pada Otak Tikus Sindrom Metabolik

Abstrak

Sindrom metabolik (SMet), beserta kelainan yang menyertainya, berkaitan dengan stres oksidatif dan inflamasi di otak yang berujung pada penurunan fungsi kognitif. Sebagai senyawa alami yang berasal dari jahe dan memiliki sifat antioksidan yang menjanjikan, 6-gingerol (6G) berpotensi menjadi kandidat terapi. Tujuan studi ini adalah untuk menyelidiki efek 6G dalam meredakan inflamasi, stres oksidatif, dan sinyal insulin di jaringan otak tikus dengan Smet. Tikus jantan Sprague-Dawley dibagi secara acak dalam lima kelompok: kontrol normal, kontrol negatif, dan tiga kelompok perlakuan yang menerima dosis 6G yang semakin meningkat selama 8 minggu. MetS diinduksi melalui pemberian diet tinggi lemak dan injeksi streptozotocin dosis rendah. Jaringan otak dianalisis untuk mengetahui kadar tumor nekrosis faktor- α (TNF- α), interleukin-1 β (IL-1 β), malondialdehid (MDA), glutathione peroksidase (GPx), glukagon-like peptide-1 (GLP-1), dan reseptor GLP-1 (GLP-1R). Studi ini dilakukan di Laboratorium Farmakokinetik Departemen Farmakologi dan Terapeutik, Fakultas Kedokteran Universitas Indonesia pada bulan Januari-Februari 2023. Kadar TNF- α secara signifikan lebih tinggi pada kelompok Smet dibandingkan dengan kelompok kontrol normal (95% CI: -4.4 – -74.9; $p = 0.024$), sedangkan tidak terdapat perbedaan yang signifikan pada kadar IL-1 β , MDA, GPx, GLP-1, dan GLP-1R antara kelompok Smet dan kelompok kontrol normal. Pemberian 6G dengan dosis 50 mg/kg/hari secara signifikan menurunkan kadar TNF- α dibandingkan dengan kelompok Smet (95% CI: -12 – -82; $p = 0.006$), sedangkan 6G dengan dosis 100 dan 200 mg/kg/hari tidak memperbaiki semua parameter. Temuan saat ini menunjukkan bahwa 6G, terutama pada dosis 50 mg/kg, memiliki efek antiinflamasi pada peradangan otak yang dipicu oleh Smet. Namun, pentingnya optimalisasi dosis untuk potensi penerapan klinis 6G masih memerlukan penelitian lebih lanjut.

Kata kunci: 6-gingerol, antidiabetik, antioksidan, otak, sindrom metabolik.

Introduction

Metabolic Syndrome (MetS) is a major health issue globally. It is estimated that 21.66% of Indonesians meet the criteria for MetS.¹ MetS is characterized by a cluster of metabolic abnormalities, including dyslipidemia, central obesity, hypertension, and hyperglycemia. These abnormalities are closely associated with heightened risks of cardiovascular diseases and type 2 diabetes mellitus.^{2,3} Furthermore, new studies have also revealed its association with cognitive decline, particularly in middle-aged and elderly populations, which manifests as a decrease in executive cognitive functioning, attention, memory, and language processing.⁴⁻⁶

Recent evidence suggests a strong association between MetS and cognitive decline. One prominent yet strong hypothesis poses that prolonged systemic inflammation may contribute to the development of what has been termed “metabolic syndrome brain”.⁶ This has been proven with observations of increased levels of many pro-inflammatory cytokines, such as C-reactive protein (CRP), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α).^{2,3} As a susceptible organ to inflammation, the brain then activates many cellular pathways, which will result in the formation of reactive oxygen species (ROS) and their residues, such as malondialdehyde (MDA), a product of lipid breakdown in tissues.^{7,8} Inhibition of the Nrf-2 pathway, mediated by long-term oxidative stress, results in a reduction of many enzymatic antioxidants, especially glutathione peroxidase (GPx), the most abundant cytoplasmic antioxidant in the brain.⁹⁻¹¹ This then puts the brain at risk of further damage, leading to cognitive decline.

Current pharmacological treatments may be used to control each metabolic abnormality to prevent cognitive decline. However, understanding the underlying pathophysiology suggests that antioxidants and antidiabetics with a direct effect on the brain might be more beneficial. Antioxidants, such as 6-gingerol (6G) from ginger, possess potential therapeutic effects.

6G has been shown to decrease ROS and balance antioxidant levels in various organs of metabolic syndrome rat models.^{7,12,13} Moreover, recent studies have established a correlation between increased plasma levels of glucagon-like peptide-1 (GLP-1), an insulin secretagogue hormone, and the administration of 6G in diabetic rat models.¹⁴ With this in mind, its receptor, the GLP-1R, may also have therapeutic potential for 6G, especially with new evidence linking its neuroprotective effects in the brain. This idea stems from evidence that its antidiabetic properties decline under chronic oxidative stress and inflammation, as observed in various pathologies.¹⁵⁻¹⁷

However, specific research, especially focusing on the MetS model, remains limited, particularly given the potential of 6G to modify anti-inflammatory, antioxidant, and antidiabetic signaling in the MetS brain. This study aims to interpret the effects of 6G on brain tissues by measuring the neuroprotective and neurotoxic parameters mentioned above.

Methods

Reagents and Materials

Purified 6G extract was obtained from Actin Chemicals®, Chengdu, China. Streptozotocin (U-9889, CAS 18883-66-4) was obtained from Santa Cruz Biotechnology, Texas, USA. ELISA kits were used to measure several markers, including rat GPx (Catalog No: ER0274) and rat GLP-1 (Catalog No: ER0996), purchased from Wuhan Fine Biotech Co., Ltd., Hubei, China. The ELISA kit used to measure rat GLP-1R levels (Catalog No. E0918Ra) was purchased from Shanghai Korain Biotech Co., Ltd., Shanghai, China. The ELISA kits used to measure rat TNF- α (Catalog No: E-EL-R2856) and rat IL-1 β (Catalog No: E-EL-R0012) were obtained from Elabscience Bioinnovation Inc., Texas, USA. Other reagents outside the kits and supplementary materials used in this study were sourced commercially and chosen by the authors according to quality standards.

Animal Models and Study Design

Adult male Sprague-Dawley Rats (n = 20; 7 weeks old) were obtained from the National Agency of Drug and Food Control (BPOM RI), Jakarta, Indonesia, and weighed 180-200 g. Before intervention, the rats were acclimated under standard conditions for one week with 25-30 °C housing temperature, 75% humidity, and a 12-hour light-dark cycle inside plastic cages. During this period, the rats received standard conventional diets and had routine daily body weight measurements. Daily food intake was calculated as the amount of food each day, given 25 grams per rat, minus the leftovers found the next day.

After one week, the rats were randomly assigned to five groups: (1) the healthy control group, (2) the negative control (MetS) group, and three intervention groups. Each group consists of 4 rats. The standard commercial diet was continued in the control group. At the same time, the remaining animals received a high-fat, high-fructose (HFHF) diet from the Universitas Brawijaya Laboratory in Malang, Indonesia, for 8 weeks. Groups 2 to 5 then received a single intraperitoneal injection of 22 mg/kg streptozotocin to induce insulin resistance. Measurements of metabolic parameters were performed in all groups to assess for metabolic syndrome, including HOMA-IR, Lee obesity index, triglycerides, lipids, and fasting glucose levels.

Confirmed MetS rats in the intervention groups then received 6-gingerol (6G) orally at 50, 100, and 200 mg/kg body weight, consecutively, for another 8 weeks. The 6G dose used in this study was based on a previous study conducted we conducted.⁷ Sacrifice was done under anesthesia with a ketamine/xylazine (300 mg/kg-30 mg/kg) injection at week 16 of the study, and brain tissues were taken for analysis. The entire process was done during a previous study performed with the ethical clearance from the Animal Care and Use Committee of Universitas Indonesia, with approval number as follows: KET-945/UN2.F1/ETIK/PPM.00.02/2021.⁷

Sampling and Biomarker Analysis

Three hundred milligrams of tissue were collected from each brain and prepared into separate homogenates. These homogenates were then centrifuged at 3000 rpm for 10 minutes at 4 °C. The resulting supernatants were then taken for subsequent measurements. MDA analysis was performed using the Thiobarbituric Acid Reactive Substances (TBARS) assay, coupled with the Bradford method for protein measurements. On the other hand, levels of TNF- α , IL-1 β , GPx, GLP-1, and GLP-1R were measured using the ELISA kits mentioned above, according to the protocols provided with each kit.

Interpretations were done by the colorimetric method using a Perkin Elmer UV/VIS λ -25 Spectrophotometer at different wavelengths. Absorbance readings for TNF- α , IL-1 β , GPx, GLP-1, and GLP-1R were obtained at 450 nm wavelength. Readings for MDA were obtained at 540 nm.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26. Data are presented as mean $\pm$ SD. The normality of data distribution was assessed using the Shapiro-Wilk test. For normally distributed data, differences among groups were analyzed using one-way ANOVA followed by Tukey's post hoc test. For non-normally distributed data, comparisons among groups were performed using the Kruskal-Wallis test followed by the Mann-Whitney U test for pairwise comparisons. A p-value < 0.05 was considered statistically significant.

Results

Effect of 6-Gingerol on TNF- α and IL-1 β Levels

As shown in Fig. 1A, TNF- α levels were significantly higher in the MetS group than in the normal group (95% CI: -4.4 to -74.9; p = 0.024); administration of a 6G dose of 50 mg/kg significantly reduced these levels compared to the MetS group (95%CI: -12 to -82; p = 0.006). Conversely, the highest IL-1 β levels were

observed in the 6G 100 mg/kg group, and this result differed significantly from that of the normal group (95%CI: -0.4 to -7.7; $p = 0.02$) and the 6G

50 mg/kg group (95%CI: -0.1 to -7.3; $p = 0.04$) (Fig. 1B).

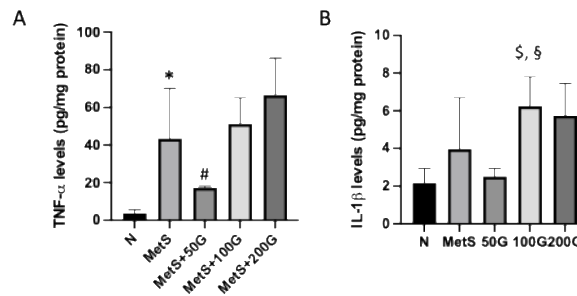


Figure 1. Differences of (A) TNF- α and (B) IL-1 β levels in the brain tissue across MetS and 6G-treated groups. Data are expressed as means $\pm$ SD ($n = 4$ in each group). * $p < 0.05$ vs N; # $p < 0.05$ vs MetS, \$ $p < 0.05$ vs N, § $p < 0.05$ vs MetS+50G

Effect of 6-Gingerol on MDA and GPx Levels

6-gingerol did not lower MDA levels or increase GPx levels at doses of 50, 100, and 200 mg/kg. MDA and GPx levels tended to be higher

in the MetS group than in the normal group, although the difference was not statistically significant (Fig. 2A and 2B).

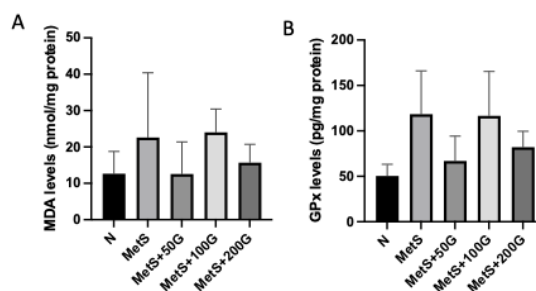


Figure 2. Differences of (A) MDA and (B) GPx levels in the brain tissue across MetS and 6G-treated groups. Data are expressed as means $\pm$ SD ($n = 4$ in each group)

Effect of 6-Gingerol on GLP-1 and GLP-1R Levels

6-gingerol did not increase GLP-1 and GLP-1R levels in the brain tissue of MetS rats at doses of 50, 100, and 200 mg/kg. Both levels tended to

be higher in the MetS group compared to the normal group, although this difference was not statistically significant (Fig. 3A and 3B).

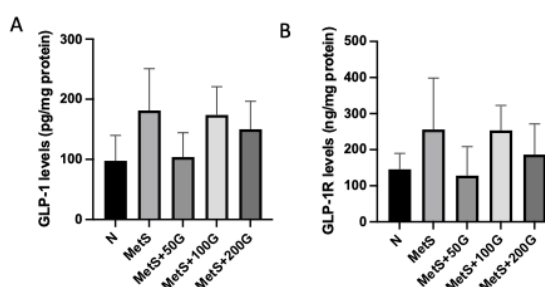


Figure 3. Differences of (A) GLP-1 and (B) GLP-1R levels in the brain tissue across MetS and 6G-treated groups. Data are expressed as means $\pm$ SD ($n = 4$ in each group)

Discussion

MetS serves as a systemic catalyst for brain dysfunction by fostering chronic inflammation and oxidative stress, resulting in neurodegeneration, cognitive decline, and heightened susceptibility to dementia or stroke.⁴⁻⁶ Elevated obesity and insulin resistance augment ROS, compromising the blood-brain barrier and stimulating astrocytes to shift to a pro-inflammatory phenotype, leading to neuronal damage.^{6,10} In this study, we found that feeding rats a high-fat diet for 16 weeks led to increased inflammation in brain tissue, as indicated by a significant increase in TNF- α levels compared to rats in the normal-control group. However, this was not accompanied by an increase in IL-1 β levels. This finding contradicts previous research demonstrating that chronic metabolic stress and adipose tissue dysfunction increase both TNF- α and IL-1 β levels, thereby triggering vascular and cognitive complications.^{18,19} During the acute inflammatory process, TNF- α synthesis increases in the early phase, within the first few hours following injury.²⁰ In addition, *in vitro* studies on mononuclear cells incubated with lipopolysaccharides also demonstrate that, within 1 hour of incubation, TNF- α levels rise in the extracellular fluid, whereas IL-1 β levels increase after 6 hours of incubation.²¹ The increase in TNF- α without a corresponding increase in IL-1 β levels in our study is most likely due to the inflammatory process still being in the acute phase. We also observed that following administration of 6G at 50 mg/kg, levels of both TNF- α and IL-1 decreased compared with the MetS group. However, 6G doses of 100 and 200 mg/kg did not reduce the levels of these two pro-inflammatory cytokines. In fact, the reduction of TNF- α levels in the brain tissue of high-fat diet-induced MetS rats by 6G at a dose of 50 mg/kg/day was consistent with our previous study in serum and liver tissue, in which the 50 mg/kg dose also exhibited greater anti-inflammatory effects compared with the 100 and 200 mg/kg doses.⁷ These findings suggest that the anti-inflammatory activity of 6G may not follow a linear dose-dependent pattern. Natural compounds such as 6G frequently exhibit biphasic or hormetic

dose-response characteristics, in which low doses produce optimal biological effects. In contrast, higher doses may reduce efficacy or trigger compensatory responses.²² At lower concentrations, 6G may effectively suppress inflammatory signaling pathways such as NF- κ B activation and proinflammatory cytokine production. However, at higher doses, receptor saturation, altered cellular adaptation, or feedback regulatory mechanisms may attenuate these beneficial effects.²³

It is well known that a diet high in fat and carbohydrates can increase oxidative stress in various cells and tissues throughout the body, including the brain.¹⁰ It is this imbalance between ROS production and enzymatic antioxidants in the body that causes oxidative stress.¹⁰ MDA is a secondary product of the peroxidation of long-chain fatty acids and is widely used as a biomarker of lipid peroxidation rates in tissues.²⁴ In our previous study, it was demonstrated that there was an increase in MDA levels and a decrease in GPx levels in the kidney and pancreas tissue of rats with MetS.^{12,13} Previous studies have also demonstrated both increases and decreases in MDA and GPx levels in brain tissue under various conditions involving oxidative stress.^{12,25,26} However, in the present study, we observed that in brain tissue from MetS rats, there were no significant differences in either MDA or GPx levels, although there was a tendency for both to be elevated in the MetS group compared to the normal-control group. This is likely because the process is still in its acute phase, characterized by elevated GPx levels to counteract ongoing oxidative stress.²³ 6-gingerol administration at any dose in our study did not attenuate oxidative stress in the brain tissue of MetS rats. Gingerol and shogaol are polyphenols that vary in distribution and concentration throughout body tissues. Peak concentrations of active ginger compounds, such as 6-shogaol and zingerone, in the brain are much lower than in other organs like the spleen and kidneys, with the highest concentrations found in the stomach, intestines, liver, and lungs. Furthermore, concentrations of these compounds decrease

about 3 hours after peak levels are detected, with rapid elimination through the liver and kidneys and a relatively short half-life of about 2,5 hours.^{27,28}

Reduced GPx activity could indicate either increased oxidative stress or decreased expression and synthesis of the enzyme in cells. Current literature suggests that the synthesis of enzymatic antioxidants, including GPx-1, is mediated by Nrf-2 transcription.^{29,30} However, Boyuk et al³¹ proposed that other factors involved in enzyme synthesis, particularly in the brain, include the secretion of Brain-Derived Neurotrophic Factor (BDNF), which supports nerve survival and is believed to have protective effects against oxidative stress through various mechanisms, including Nrf-2 activation.³¹

Boyuk et al³¹ and Suwa et al³² observed increased BDNF levels in newly diagnosed diabetes patients, with Boyuk et al. specifically reporting significant differences in BDNF levels compared to control groups with lower body mass index, blood pressure, and HbA1c values. This indicates elevated BDNF levels during early metabolic changes in the progression of MetS.^{31,32} Recent literature concludes that BDNF levels depend strongly on the duration of MetS, especially in the context of chronic hyperglycemia.³³

Cut-offs for defining “chronic hyperglycemia” remain a matter of debate. A study long ago showed that GPx levels decline over time with sustained hyperglycemia. This relationship appears to be more pronounced among inbreds. Such findings may reflect underlying genetic aberrations across generations in MetS rat models.³³ One possible explanation may involve BDNF-mediated neuroprotective mechanisms, although this parameter was not evaluated in the present study. We therefore hypothesized that 8 weeks of HFHF diet might not be adequate to induce “overt hyperglycemia”, considering BDNF and Nrf-2 interactions could still confer neuroprotective effects against oxidative stress in early metabolic syndrome brain.

This study also examines the impact of an HFHF diet on GLP-1 and its receptor, GLP-1R, levels in the brain, as well as the potential role of 6G as an intervention to modulate these

parameters. GLP-1, an essential hormone primarily synthesized in the gastrointestinal tract, is known to regulate appetite, energy balance, and insulin secretion.³⁴⁻³⁶ Although GLP-1 reduces hunger and aids weight loss, it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), leading to a short half-life. By comparing healthy control rats with those on an HFHF diet, this study reveals an increase in GLP-1 and GLP-1R levels among HFHF-fed rats, potentially due to the conversion of fructose into glucose in the liver, which raises GLP-1 levels and enhances insulin release.^{37,38} This dietary model also appears to alter the nutrient-sensing functions of L-cells in the gastrointestinal tract, increasing their sensitivity and potentially slowing the onset of glucose intolerance and obesity. Furthermore, modifications in GLP-1R levels in HFHF-fed rats indicate that GLP-1 receptor islets may play a significant role in enhancing insulin secretion and preventing insulin resistance in peripheral tissues.³⁹

In exploring the connection between HFHF diets, cognitive impairment, and metabolic syndrome, the study highlights the systemic effects of HFHF-induced metabolic syndrome, which include disrupted glycemic control, increased oxidative stress, and neuroinflammation. The HFHF diet was associated with an upregulation of the proglucagon gene in the brainstem, increasing GLP-1 production and activating protein kinase A (PKA) and protein kinase C (PKC) pathways, thus impairing insulin sensitivity.⁴⁰ Chronic HFHF diets have also been linked to neuroinflammation and neurodegeneration, with astrocytes and microglia displaying adaptive changes in response to elevated pro-inflammatory cytokines crossing the BBB.⁴⁰ Peripheral inflammation in metabolic syndrome appears to trigger oxidative stress, leading to mitochondrial dysfunction and decreased energy supply to synaptic mitochondria, which may contribute to cognitive decline. Astrocytes, as responsive cells in the brain, initially play a neuroprotective role by releasing heat shock proteins and neurotrophic factors. Still, prolonged exposure to the HFHF diet eventually overwhelms these protective

mechanisms, reducing astrocyte efficacy and increasing neurodegeneration.^{41,42}

However, only a small fraction of GLP-1 synthesized in the intestine reaches the brain, where GLP-1R expression is limited to specific clusters of neurons in the caudal nucleus of the solitary tract and the ventrolateral medulla.³⁹ This restricted distribution highlights the distinct peripheral and central roles of GLP-1. While peripheral GLP-1 activity is crucial for metabolic regulation, central GLP-1 receptors contribute to appetite control and neuroprotection.³⁵ This finding supports the hypothesis that 6G's central effects may be limited due to its restricted bioavailability in the brain, whereas its peripheral effects on metabolic regulation are more pronounced.

Strengths of this study include the use of a specific HFHF-induced rat model designed to simulate the features of the metabolic syndrome brain. This study also used different doses of 6G to explore potential dose-dependent effects on multiple parameters representing distinct molecular pathways, including the inflammatory, oxidative, and metabolic pathways. However, this study was not conducted over a long period to assess these changes, which may be a confounding factor in this design. The duration of the HFHF trial should be sufficient to induce adequate breakdown of the blood-brain barrier secondary to chronic inflammation, which represents the true metabolic syndrome brain. This process would then confer a permissive effect, allowing 6G to accumulate to an adequate concentration in the brain. The dose range in this study may be expanded to increase its potency in the brain. Another limitation is the relatively small sample size ($n = 4$ per group), which may limit statistical power. Another limitation of this study is the absence of histopathological analysis of brain tissue, which could have provided stronger morphological evidence of neuroinflammation and of astrocyte transformation into a pro-inflammatory phenotype. In addition, the absence of behavioral or cognitive function assessments limits the ability to determine whether the observed reduction in neuroinflammatory markers

was associated with improvements in cognitive impairment or neurological function.

Conclusion

In conclusion, 6G at 50 mg/kg/day for 8 weeks significantly reduced TNF- α levels in the brain tissue of rats with MetS, whereas higher doses (100 and 200 mg/kg/day) did not show a similar effect. This finding may reflect a hormetic dose-response pattern, which is commonly observed in natural bioactive compounds, where lower doses exert more favorable biological effects than higher doses. Dose optimization is essential for translating these findings.

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Authors' Contributions

VS formulated the research question, designed the experiment, and gathered the necessary materials. KR, TA, and AZ performed the experiments, conducted the data analysis, and wrote the manuscript, with additional scientific advice from VS. All authors contributed to the manuscript and performed critical revisions. All authors reviewed and approved the final version of the manuscript.

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Data and Materials Availability

All raw data from the experiment are available in Appendix 1.

Ethics Statement

Every aspect of the study was conducted in accordance with the Declaration of Helsinki and international ethical guidelines. Ethical clearance was received from the Animal Care and Use Committee of Universitas Indonesia, with approval number: KET-945/UN2.F1/ETIK/PPM.00.02/2021.

Consent for Publication

This study does not include any personal data or identifiable images.

Competing Interests

The authors declare that they have no known financial interests or personal relationships that could have influenced the results reported in this manuscript.

AI Usage Declaration

Grammarly AI was used to correct grammar mistakes

after the complete manuscript was written, with minimal reconstruction of the original sentences or paragraphs. All content has been reviewed, verified, and approved by the authors, and full responsibility for the manuscript remains with the authors.

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