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Therapeutic Potential of *Kaempferia galanga* L. Extract in Ameliorating Oxidative Stress and Metabolic Dysregulation in a Rat Model of Metabolic Syndrome

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Abstract
Metabolic syndrome is associated with an increased risk of hypertension, diabetes, and cardiovascular disease, which are often triggered by oxidative stress and inflammation. This study evaluated the effects of *Kaempferia galanga* L extract (ERK) on oxidative stress and metabolic dysfunction using a fructose-induced male Wistar rat model. A total of 25 rats were divided into five groups: normal control, positive control, allopurinol group, and two ERK treatment groups at doses of 50 and 100 mg/kg body weight. All groups, except the normal control, were given 25% fructose in the drinking water and an injection of potassium oxonate (4.5 mg/kg body weight) for 28 days. Evaluation was done by measurement of glucose, triglyceride, malondialdehyde (MDA) and nitric oxide (NO) and histological analysis of aortic tissue. The results showed that ERK, especially at a dose of 100 mg/kg, significantly reduced glucose, triglyceride and MDA levels and increased NO levels. ERK administration also reduced the body weight of mice and prevented the formation of foam and inflammatory cells in aortic tissue. The total flavonoid content of ERK also supports its biological activity. This study concludes that ERK has potential as a natural therapeutic agent to treat metabolic syndrome through antioxidant and anti-inflammatory mechanisms.

Keywords: *Kaempferia galanga* L., oxidative stress, metabolic syndrome, nitric oxide, malondialdehyde.

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Potensi Terapi Ekstrak *Kaempferia galanga* L. dalam Memperbaiki Stres Oksidatif dan Disregulasi Metabolisme pada Tikus Model Sindrom Metabolik

Abstrak
Sindrom metabolik berhubungan dengan peningkatan risiko hipertensi, diabetes, dan penyakit kardiovaskular, yang sering dipicu oleh stres oksidatif dan peradangan. Penelitian ini mengevaluasi efek ekstrak rimpang kencur (ERK) terhadap stres oksidatif dan disfungsi metabolik menggunakan model tikus Wistar jantan yang diinduksi fruktosa. Sebanyak 25 ekor tikus dibagi menjadi lima kelompok: kontrol normal, kontrol positif, kelompok allopurinol, serta dua kelompok perlakuan ERK dengan dosis 50 dan 100 mg/kg BB. Semua kelompok, kecuali kontrol normal, diberikan 25% fruktosa dalam air minum selama 28 hari dan satu kali injeksi kalium oksonat (4,5 mg/kg bobot badan). Evaluasi dilakukan melalui pengukuran glukosa, trigliserida, malondialdehida (MDA), dan oksida nitrat (NO), serta analisis histologi jaringan aorta. Hasil menunjukkan bahwa ERK, terutama pada dosis 100 mg/kg, secara signifikan menurunkan kadar glukosa, trigliserida, dan MDA, serta meningkatkan kadar NO. Pemberian ERK juga menurunkan bobot badan tikus dan mencegah terbentuknya sel busa dan inflamasi di jaringan aorta. Kandungan flavonoid total dalam ERK turut mendukung aktivitas biologisnya. Penelitian ini menyimpulkan bahwa ERK berpotensi sebagai agen terapeutik alami untuk menangani sindrom metabolik melalui mekanisme antioksidan dan antiinflamasi.

Kata Kunci: *Kaempferia galanga* L., malondialdehid, nitrit oksida, sindrom metabolik, stres oksidatif

1. Introduction

Metabolic syndrome is a physiological disorder that heightens the likelihood of developing non-communicable diseases. This condition is defined by multiple factors, including central obesity, high triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C), high blood pressure, and reduced insulin responsiveness1. The key elements assessed in all metabolic syndrome criteria, as defined by the International Diabetes Federation (IDF), the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III), and the World Health Organization (WHO), encompass the measurement of insulin resistance, heightened blood glucose levels, abnormal lipid profiles, excessive adiposity, and elevated blood pressure.[2]

Based on IDF statistics from 2018, metabolic syndrome affects 20-25% of the global population3. The 2018 Basic Health Research (RISKESDAS) reveals that the prevalence of metabolic syndrome in Indonesia surpasses the global average, with regional variations. The rates range from 22.22% in Papua to 44.13% in South Kalimantan, with other regions falling between these extremes: Jakarta (33.43%), West Java (39.60%), Bali (29.97%), West Kalimantan (36.99%), North Sulawesi (31.68%), and South Sumatra (30.44%). A notable disparity exists between urban and rural areas, with urban regions exhibiting a higher prevalence at 17.5%. This urban-rural difference is attributed mainly to lifestyle factors, including dietary habits, insufficient physical activity, alcohol consumption, and environmental conditions4. Oxidative stress and inflammation play a crucial role in the emergence of metabolic syndrome. These factors contribute to endothelial dysfunction and disrupt the synthesis of nitric oxide (NO), which is vital for proper cardiovascular functioning.[5]

Addressing metabolic syndrome through a symptom-by-symptom approach is currently considered suboptimal. The administration of numerous conventional drugs raises concerns about patient adherence and potential adverse reactions. Allopurinol, a medication under investigation for its positive effects on metabolic syndrome, has shown promise in research studies. Specifically, it has demonstrated the ability to improve hepatic steatosis induced by excessive fructose consumption by modulating pathways associated with lipid metabolism, inflammatory processes, and stress in the endoplasmic reticulum6. Nevertheless, allopurinol induces severe adverse reactions that lead to patient non-adherence, including cutaneous eruptions, decreased white blood cell count, digestive system disturbances, and hives.[7]

Given these challenges, an alternative approach to addressing metabolic syndrome involves utilizing herbal remedies. The rationale for adopting multi-target botanical therapies is based on their low side effect profile, non-toxic nature, and demonstrated efficacy and effectiveness.[8] As a safer and more effective alternative to conventional treatments, herbal therapies for metabolic syndrome may enhance patient adherence to prescribed regimens.

The kencur rhizome (*Kaempferia galanga*), a member of the Zingiberaceae family, is believed to possess inhibitory effects against metabolic syndrome. This plant contains several bioactive compounds, including ethyl p-methoxycinnamate (EPMS), pentadecana, and kaempferol, which contribute to its potential therapeutic properties9. EPMS also demonstrates additional pharmacological properties, including its function as an antidiabetic agent[10], anti-inflammatory,[11,12] and vasorelaxant.[13]

Earlier studies have demonstrated the antidiabetic properties of kencur rice, evidenced by reduced blood sugar levels, weight management, and enhanced condition of Langerhans islets in the pancreas of rats induced with streptozotocin.[14] The research by Yuk *et al*., (2018) also tested the anti-inflammatory effects of kencur rhizomes extract in an obese rat animal model, the results showed that the extract could reduce the production of TNF-α and IL-1β.[15] In addition, it is supported by research by Chen *et al*., (2018) which tested the effect of *Kaempferia parviflora* extract on hyperuricemia rats showing a decrease in uric acid levels.[16]

This research is important due to the widespread consumption of kencur rhizomes in Indonesia and their pharmacological activity in inhibiting metabolic syndrome. The study aims to determine the appropriate dosage for effective use in addressing metabolic syndrome.

2. Materials and Methods

2.1. Tools

The tools used are micropipettes (DragonLab®), pH meters (Mettler Toledo®), ELISA microplate readers (BioTek 800TS®), UV-Vis spectrophotometers (Shimadzu®), and photometers (Microlab 300®).

2.2. Materials

The ingredients used are kencur thick extract (*Kaempferia galanga* L.), CMC-Na (Merck®), allopurinol (Hexpharm Jaya®), potassium oxonate (Aldrich®),

fructose (Merck®), dan reagent uric acid (ProLine®), reagent triglycerides (ProLine®), reagent glucose (ProLine®), enzyme xanthine oxidase (Sigma®), substrate xanthine (Sigma®), HCl, H_2SO_4, aquadest, quercetin (Sigma®), acetate acid anhidrat, magnesium powder, ammonia, chloroform, buffer phosphate, buffer Tris HCl, NaOH, N-(1-Naphthyl) ethylenediamine dihydrochloride (Merck®), sodium acetate anhydrate, NaCl Physiological (Otsuka®), Trichloroacetic acid (TCA), 2-Thiobarbituric Acid (TBA), Ferrous sulfate heptahydrate ($FeSO_4.7H_2O$).

2.3. Methods

2.3.1. Preparation of Kencur Rhizomes Extract

The kencur (*Kaempferia galanga*) rhizome was obtained from the BPSI TROA (Standard Testing Center for Spice, Medicinal, and Aromatic Plant Instruments) in Bogor, West Java. Plant identification was performed at UNPAD's (Padjajaran University) Plant Taxonomy Laboratory, which is part of the Biology Department in the Faculty of Mathematics and Natural Sciences (FMIPA). The reference number for this identification was 31/HB/02/2024.

The process began with the selection and grinding of 2 kg of dried kencur rhizomes to create a fine powder. Extraction was performed using the maceration technique, employing 96% ethanol as the extracting agent. Following maceration, the solution was strained to obtain the liquid extract. This extract was subsequently concentrated using a rotary evaporator, maintaining a temperature between 40-45°C, until a viscous extract was produced.

2.3.2. Phytochemical Screening

An analysis of secondary metabolites was performed on the 96% ethanol extract derived from *Kaempferia galanga* rhizomes to determine its potential antihyperuricemic properties. The investigation focused on detecting the presence of various compounds, including alkaloids, saponins, flavonoids, tannins, triterpenoids, and steroids.

Test for Alkaloids

An extract of 1 mL was combined with equal parts (5 mL each) of ammonia and chloroform. The mixture was then heated, agitated, and filtered. To each resulting filtrate, approximately 5 drops of 2N H_2SO_4 were introduced, followed by agitation and settling. Subsequently, the upper layer of each filtrate underwent testing using Mayer's, Wagner's, and Dragendorff's reagents. The presence of alkaloids was indicated by the formation of precipitates in white, brown, or orange colors.

Test for Flavonoids

The extract (1 mL) was combined with 70% ethanol (3 mL) and subjected to homogenization and heating, followed by another round of homogenization and filtration. The resulting filtrate was subsequently combined with magnesium powder (0.1 g) and concentrated HCl (2 drops). The development of a red hue in the ethanol layer signified the presence of flavonoids.

Test for Saponins

Into a test tube, 1 mL of extract was introduced, followed by the addition of 10 mL of heated water. After allowing the mixture to cool down, it was vigorously agitated for 10 seconds. The formation of persistent foam, measuring 1–10 cm in height and lasting for at least 10 minutes, indicated the presence of saponins. The stability of the foam was confirmed when it remained intact after the introduction of a single drop of 2N HCl.

Test for Tannins

The sample was solubilized in purified water, then treated with 3 drops of $FeCl_3$ solution. A shift in color to either dark green or deep blue indicated the presence of tannins.

Test for Terpenoids and Steroids

The presence of steroids and terpenoids was determined by combining 1 mL of extract with 3 mL of either chloroform or 70% ethanol. Subsequently, 2 mL each of concentrated sulfuric acid and acetic anhydride were added to the mixture. The detection of steroids was indicated by a color shift from purple to blue or green, while the formation of a brownish hue at the interface signaled the presence of terpenoids.

2.3.3. Total Flavonoid Content

The procedure involved combining 100 µL of extract with 4 ml of distilled water. Subsequently, 0.3 ml of 5% sodium nitrite was introduced. Following a 5-minute interval, 0.3 ml of 10% aluminum chloride was added. After 6 minutes, 2 ml of 1 M sodium hydroxide was incorporated into the mixture. The solution was then promptly diluted with 3.3 ml of distilled water and thoroughly mixed. Absorbance measurements were taken at 510 nm against a blank sample. A calibration curve was established using catechin as the standard. The total flavonoids content in the extract was quantified and expressed as milligrams of catechin equivalents per gram of sample (mg/g).

2.3.4. Treatment of Experimental Animals

This study employs a true experimental design, specifically a pretest-only control group approach, which involves taking measurements before and after treatment administration.

The experiment utilized 25 male Wistar rats, aged 2-3 months and weighing between 200-300 g. These rats were randomly divided into five groups of 5 animals each. The experimental groups were categorized as follows:

1. Normal: Received 0.5% CMC-Na
2. Positive: Administered 0.5% CMC-Na and subjected to potassium oxonate induction at 4.5 mg/kg body weight
3. Allopurinol: Given Allopurinol suspension (1.8 mg/kg body weight) and subjected to potassium oxonate induction at 4.5 mg/kg body weight
4. ERK 50: Treated with Kencur Extract (50 mg/kg body weight) and subjected to potassium oxonate induction at 4.5 mg/kg body weight
5. ERK 100: Provided with Kencur Rhizomes Extract (100 mg/kg body weight) and subjected to potassium oxonate induction at 4.5 mg/kg body weight.

Following group allocation, the experimental animals underwent a 10-day acclimation period with free access to standard diet and water. Any animals that became sick, perished, or experienced weight loss exceeding 10% were removed from the study. The animal housing was maintained in a clean condition, with environmental parameters set at 24-26°C for temperature, 70-75% for humidity, and a light-dark cycle alternating every 12 hours.

The rats underwent a 10-day adaptation period before being separated into five experimental groups. The study spanned 28 days, during which regular feed was supplied, and all groups except the control were given 25% fructose water to drink freely. Initial triglyceride and glucose measurements were taken on day 0 (t0). On the final day (t28), potassium oxonate was administered to all groups except the control. Triglyceride and glucose levels were reassessed in all groups one hour after the induction.

2.3.6. Glucose and Trglyceride Level Examination

The weight of the rats was recorded on days 0, 7, 14, and 28. Triglyceride and glucose levels were analyzed using the GPO-PAP and GOD-PAP methods. Blood was collected via orbital sinuses with hematocrit capillary tubes, then centrifuged for 5 minutes at 3000 rpm to obtain serum.

To conduct the analysis, a 5 µl plasma sample was extracted using a micropipette and placed in a separate container. Subsequently, 500 µl of enzymatic reagents for triglycerides and glucose (both ProLine®) were introduced to the sample. The resulting mixture was then left to incubate for 20 minutes at a temperature between 20-25°C. Following incubation, the samples were analyzed using a Microlab 300 photometer set to a wavelength of 546 nm. The blank absorption was documented within a 60-minute timeframe.

2.3.7. Nitric Oxide Levels Measurement

Rat blood serum (600 µL) was combined with 6% ZnSO4 (80 µL) and subjected to centrifugation at 5000 rpm for 30 minutes, resulting in a pink protein precipitate. Subsequently, 400 µL of the protein-free solution was blended with 80 µL of cadmium and left to incubate at 25°C for 15 minutes. Following this incubation period, 76 µL of the resulting mixture was added to 3 mL of Griess reagent and incubated at 27°C for 60 minutes. The final analysis was conducted using a UV-Vis spectrophotometer, measuring absorbance at 535 nm.[17,18]

2.3.8. Measurement of Malondialdehyde

In an Eppendorf tube, 0.6 mL of rat kidney homogenate was combined with 2.2 mL of HCl (pH 7.4). Subsequently, 0.2 mL of $FeSO_4 \cdot 7H_2O$ was added to the solution. The mixture underwent incubation at 37°C for 60 minutes. Following this period, 0.5 mL of TCA, 0.25 mL of 5N HCl, and 0.5 mL of TBA were incorporated into the sample. After homogenization, the preparation was subjected to a second incubation in a 100°C water bath for 10 minutes. Once cooled, 3 mL of chloroform was introduced, and the resulting mixture was centrifuged at 2500 rpm for 10 minutes. The supernatant was then extracted, and its absorbance was determined using a spectrophotometer set to a wavelength of 532 nm.[19,20]

2.3.9. Cardiac Aortic Histology

Cardiac samples obtained from rats in diverse experimental groups are utilized to evaluate endothelial dysfunction and conduct histopathological studies of the heart. These samples undergo a cleaning process with 0.9% NaCl solution, followed by fixation in a 10% neutral buffered formalin solution. After fixation, histopathological specimens are prepared and stained using phloxin. Microscopic examination of these preparations is performed at 100x magnification initially, then at 400x. The primary focus of these observations includes quantifying foam cells and identifying histopathological alterations, such as changes in aortic thickness, which serve as indicators of vascular inflammation.

2.3.10. Data Analysis

The Shapiro-Wilk test was employed to examine data normality, while variance homogeneity was investigated using the Levene Test. When the data exhibit both normal distribution and homogeneous variances, researchers proceed with an Analysis of Variance (ANOVA), setting the Confidence Interval at 95% (α = 0.05). ANOVA serves to compare the means across different treatments. Should significant differences emerge, a Post Hoc Test can be implemented to identify specific variations among the treatment groups.

3. Result

3.1. Phytochemicals Screening

The extraction process of kencur rhizomes (*Kaempferia galanga* L.) resulted in a concentrated substance weighing 235.8 grams, equivalent to an 11.79% yield. Phytochemical screening of the ethanol extract of kencur rhizomes revealed the presence of several secondary metabolites, including alkaloids, flavonoids, tannins, and terpenoids. These findings are consistent with previous studies that reported similar phytochemical profiles in *Kaempferia galanga*.

3.2. Total Flavonoids Content

In addition, the total flavonoid content (TFC) of the ethanol extract was quantified and found to be 7.79 ± 0.10 mg quercetin equivalents (QE) per gram of extract, indicating a substantial presence of flavonoid constituents. This relatively high flavonoid content may contribute to the extract's antioxidant and pharmacological potential. This result is supported by research that was conducted by Julianti in 2022 regarding the phytochemical screening of kencur rhizome extract. Based on these results, it showed that the phytochemical screening that has been carried out has the same results as several previous phytochemical screening studies of kencur rhizome extract.[21]

3.3. Measurement of Rats Body Weight

The positive group of rats experienced an average weight increase of 27.89% over 28 days (see Figure 1). It is noted that rats are classified as having metabolic syndrome when they exhibit a weight gain of more than 20%.[22] The theory aligns with the results observed in the positive group. The administration of ERK at doses of 50 and 100 suppressed weight gain by 10.02% and 8.50%, respectively.

3.4. Triglyceride Level Measurement

Figure 2 illustrates the changes in triglyceride levels across groups. The normal group experienced a minor elevation, with values increasing from 35.18 mg/dL at the initial measurement (T0) to 37.12 mg/dL at the final assessment (T28). In contrast, the positive group demonstrated a more pronounced upward trend, with triglyceride concentrations surging from 37.44 mg/dL at T0 to 86.68 mg/dL by T28. Statistical analysis revealed a significant difference ($p<0.05$) between the triglyceride levels of the normal and positive groups at the study's conclusion (T28).

When comparing doses of 50 mg/kgBW and 100 mg/kgBW, the effectiveness in reducing triglyceride levels was found to be greater with the 100 mg/kg BW dose of kencur rhizomes extract. This improvement is likely due to the increased dosage, which provides a stronger pharmacological effect by delivering a higher concentration of active substances in the body.

3.5. Measurement of Glucose Levels

The results of the blood glucose level measurements are presented in Figure 3. In the normal group, there was no significant change in blood glucose levels between T0 and T28. This indicates stable glucose homeostasis in rat that were not induced with fructose and potassium oxonate.

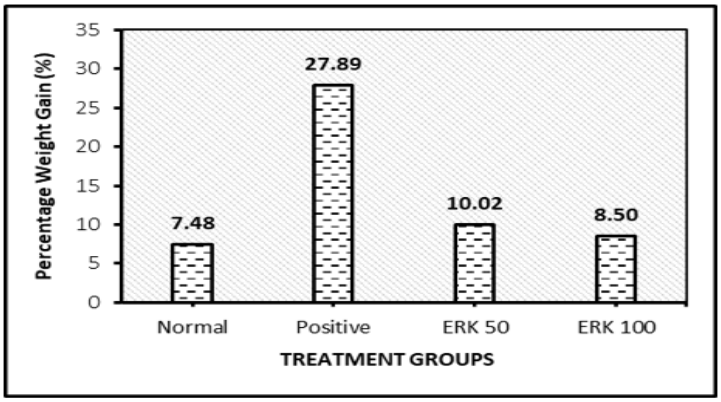

Figure 1. Percentage Increase in Body Weight of Metabolic Syndrome Rats on Day 28

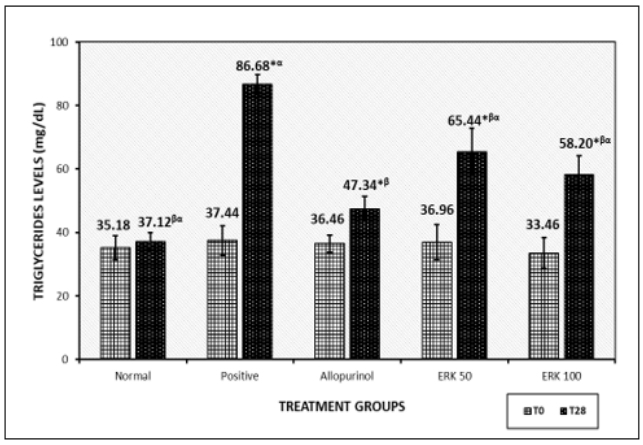

Figure 2. Measurement of Triglyceride Levels in Rats with a Metabolic Syndrome Model. (*) It was statistically significantly different from the normal group ($p<0.05$); (β) Statistically significant difference from the positive group ($p<0.05$); (α) Statistically significant difference from the allopurinol group ($p<0.05$).

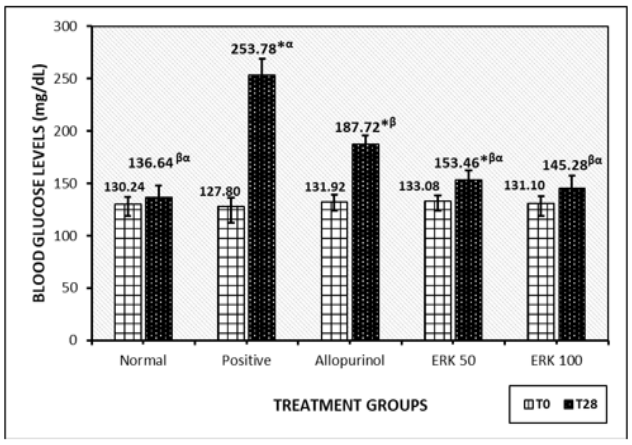

Figure 3. Measuring Glucose Levels in Rats with a Metabolic Syndrome Model. (*) It was statistically significantly different from the normal group ($p<0.05$); (β) Statistically significant difference from the positive group ($p<0.05$); (α) Statistically significant difference from the allopurinol group ($p<0.05$).

In the positive group induced by potassium oxonate, there was a significant increase in blood glucose levels from T0 to T28 ($p<0.05$), indicating that potassium oxonate induces hyperglycemia (see Figure 3). In the ERK 50 group, blood glucose levels also rose significantly from T0 to T28 ($p<0.05$) when compared to both the normal and positive groups ($p<0.05$).

Meanwhile, ERK 100 displayed slightly different results compared to ERK 50. Specifically, ERK 100 demonstrated a statistically significant difference ($p<0.05$) when compared to the positive group, but there was no statistically significant difference ($p>0.05$) when compared to the normal group, despite an average value that was higher than normal. Nonetheless, in terms of statistical outcomes, ERK 100 was effective in reducing blood glucose levels in metabolic syndrome rat, achieving results comparable to those of normal rat that did not receive any test substances.

3.6. NO Measurement

The results presented in Figure 4 indicate that the normal group differed significantly from all other groups, except for the allopurinol group ($p<0.05$), with a high NO level of 19.03 µm. The ERK 50 and ERK 100 groups also exhibited relatively high NO levels, measuring 11.24 µm and 15.42 µm, respectively, which are close to the levels seen in the allopurinol group. These findings suggest that kencur rhizome extract effectively increases NO levels. Furthermore, ERK 100 is more effective in enhancing NO levels compared to ERK 50.

3.7. MDA Measurement

In Figure 5, the results of the statistical analysis indicate that the average MDA level in the normal group of rats was 1.52 µm. This finding establishes the baseline average of MDA levels in rats under normal conditions. In contrast, the average MDA level in the positive group induced with potassium oxonate was measured at 4.64 µm. Elevated MDA levels serve as a marker for cell damage caused by lipid peroxidation.

The ERK 50 and ERK 100 groups showed average MDA levels of 3.61 µm and 2.28 µm, respectively. The MDA levels observed in ERK 100 were lower than those in the ERK 50 group. This suggests a dose-response effect, where increasing the dose may lead to a reduction in lipid peroxidation and MDA production by decreasing free radicals.[23]

3.8. Aortic Histology

The results from the aortic histological test (Figure 6) revealed the presence of foam cells and inflammatory cells in the aorta of male Wistar strain rats across all test groups. Foam cells are macrophages that contain lipids, particularly cholesterol, which gives them a foamy appearance under a microscope. In the positive group of rat heart specimens, numerous foam cells were observed among the heart muscle cells, indicating an accumulation of lipids.

4. Discussion

The research investigated the impact of kencur rhizome extract (*Kaempferia galanga* L.) on oxidative stress and metabolic disturbances in animal models

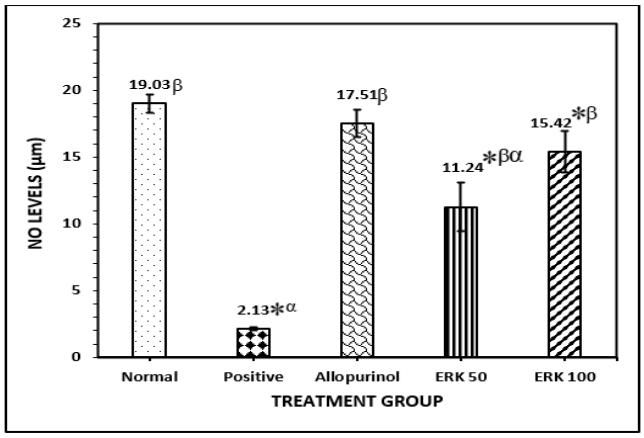

Figure 4. Measurement of NO Levels in Metabolic Syndrome Model Rats. (*) It was statistically significantly different from the normal group (p<0.05); (β) Statistically significant difference from the positive group (p<0.05); (α) Statistically significant difference from the allopurinol group (p<0.05).

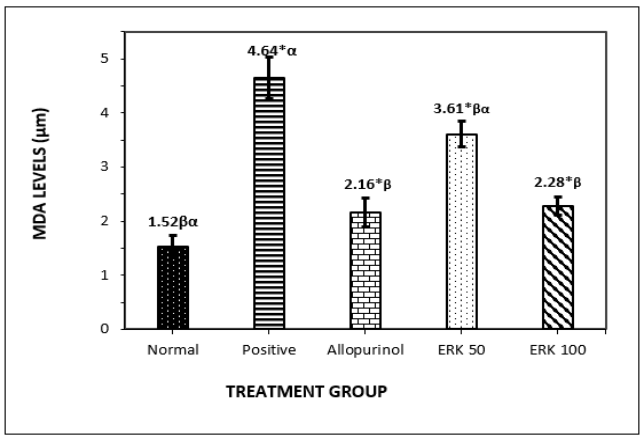

Figure 5. Measurement of Malondialdehyde (MDA) Levels. (*) It was statistically significantly different from the normal group (p<0.05); (β) Statistically significant difference from the positive group (p<0.05); (α) Statistically significant difference from the allopurinol group (p<0.05).

exhibiting metabolic syndrome. A notable decrease in triglyceride levels within the blood serum of the experimental group may be attributed to the flavonoids contained in the kencur rhizome extract.[23] The production of cholesterol can be decreased by flavonoids through their interference with HMG-CoA reductase, a crucial enzyme in the liver's cholesterol synthesis pathway. This inhibitory effect on the enzyme's function contributes to a reduction in overall cholesterol formation within the liver. Moreover, flavonoids have the ability to reduce the function of acyl-CoA cholesterol acyltransferase (ACAT), an enzyme that plays a role in managing cholesterol uptake in the intestinal tract and the synthesis of lipoproteins within the liver.[24] Flavonoids can enhance the hydrolysis of lipids by the lipase enzyme, allowing for the absorption of fatty acids, monoglycerides, and cholesterol through the intestinal mucosal cells. This process enables lipids to be excreted in the feces, leading to a decrease in cholesterol and triglyceride levels.[25]

The emergence of metabolic syndrome has been strongly linked to diets rich in fructose, which exert both direct and indirect effects. Such dietary patterns can negatively impact the performance of numerous organs and tissues throughout the body. Fructose consumption has immediate harmful effects due to its liver metabolism, which generates triglycerides and free fatty acids, potentially causing hypertriglyceridemia. Furthermore, fructose and its byproducts decrease liver ATP levels, inducing oxidative stress. This oxidative stress is linked to heightened chronic inflammation and impaired endothelial function, both of which can exacerbate metabolic syndrome.[26] The findings align with prior investigations, demonstrating that fructose consumption in the diet is associated with increased stiffness in arteries, accelerated heart rate, and the onset of hyperlipidemia.[27] The consumption of dietary fructose induces more adverse metabolic and vascular alterations compared to glucose consumption, even though glucose accounts for a greater proportion of total caloric intake than fructose.[27]

According to a study by Yamazaki *et al*. (2020), kencur rhizomes can enhance insulin sensitivity, which is crucial for regulating blood glucose and energy metabolism.[28] The enhancement occurs through the modulation of insulin signaling pathways and the heightened activity of glucose transporters, particularly GLUT4. Consequently, the rhizomes of kencur facilitate increased glucose absorption in adipose and muscle tissues, resulting in lowered blood sugar levels and enhanced metabolic efficiency. Kencur (*Kaempferia galanga* L.) possesses anti-inflammatory, antioxidant, and metabolic regulatory effects, with flavonoids and other bioactive compounds playing a role in addressing metabolic syndrome.[29,30]

An animal model of metabolic syndrome can be effectively created by combining potassium oxonate with fructose. This approach yields superior results in terms of efficiency, stability, and long-term viability when compared to the use of either compound independently.[31]

Although this study did not directly measure uric acid levels, potassium oxonate was used to induce impaired glucose and triglyceride metabolism. Potassium oxonate leads to a buildup of uric acid in the blood. Administering potassium oxonate inhibits the enzyme uricase, which is responsible for breaking down uric acid in rats. This creates a model of hyperuricemia, a condition that can lead to insulin resistance, inflammation, and oxidative stress—factors that are all

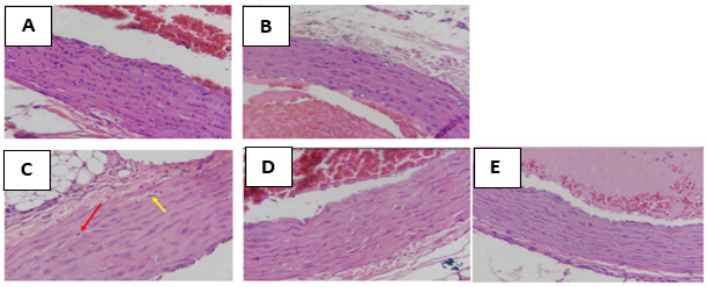

Figure 6. Aortic Histology. (A): Normal Group, (B): Comparison Group (Allopurinol), (C): Positive Group, (D): ERK Group 50 mg/kg BW, (E): ERK Group 100 mg/kg BW; Yellow Arrow: Indicates foam cells, Red Arrow: Indicates inflammatory cells.

associated with metabolic syndrome.[32,33] This increase in oxidative stress activates inflammatory pathways, contributing to metabolic dysregulation.[34]

Metabolic dysregulation caused by potassium oxonate occurs through a complex mechanism. An increase in uric acid, due to uricase inhibition, triggers oxidative stress and inflammation, which then worsens insulin resistance.[35] Insulin resistance disrupts the metabolism of glucose and lipids, leading to hyperglycemia and high triglyceride levels (hypertriglyceridemia). A diet high in fructose, combined with hyperuricemia, further worsens metabolic dysregulation. This situation creates a relevant model for studying the metabolic syndrome and exploring the potential of herbal treatments, such as *Kaempferia galanga* extract (ERK), as tested in this study.[36]

A dose of potassium oxonate at 250 mg/kgBW was used, based on a 2023 study by Afiah. This study demonstrated that this dosage effectively increases uric acid levels, which is a significant risk factor in triggering metabolic syndrome.[37]

Body weight measurements were conducted on days 0, 7, 14, and 28. This schedule was established to account for daily variability and ensure that the data collected accurately reflected the actual conditions of the research subjects.[38]

Certain substances present in Kaempferia galanga, particularly trans-ethyl p-methoxycinnamate, demonstrate potent antioxidant properties. These molecules are capable of neutralizing free radicals and decreasing reactive oxygen species (ROS), which indirectly suppresses the activation of inducible nitric oxide synthase (iNOS). The reduction of ROS leads to a decrease in oxidative stress, thereby inhibiting further iNOS induction. The expression of iNOS is primarily regulated by the NF-κB signaling pathway.[39]

Kaempferia galanga inhibits the NF-κB pathway, reducing iNOS gene transcription and pro-inflammatory cytokine production. It also enhances antioxidant enzyme activity (SOD, CAT, GPx), lowering reactive oxygen species (ROS) levels and reducing the need for iNOS induction in response to oxidative stress.[40]

Hyperglycemia occurs when blood glucose levels rise beyond normal limits, primarily due to the body's absorption of excess glucose. When glucose consumption is too high, the β cells in the pancreas are unable to produce insulin effectively, leading to elevated blood glucose levels.[41] Fructose administration was chosen because 25% fructose, compared to 25% glucose, can increase *de novo lipogenesis* and visceral *adiposity*, promote dyslipidemia, and decrease insulin sensitivity.[42]

Fructose administration can lead to insulin resistance through two main pathways. The first pathway involves the formation of uric acid. When fructose is metabolized in the body, the enzyme ketohexokinase (KHK) phosphorylates it using ATP, which leads to the formation of uric acid. Increased levels of uric acid reduce nitric oxide (NO) levels, which causes blood vessels to constrict and decreases glucose uptake in tissue cells. Moreover, uric acid can lead to an increase in free radicals in the body, causing an imbalance between free radicals and antioxidant defenses. This imbalance ultimately results in insulin resistance.[43]

The second pathway involves de novo lipogenesis (DNL), where fructose can stimulate DNL by supplying carbon atoms, specifically via CoA and glycerol-3-phosphate. These components are converted into monoacylglycerol and diacylglycerol (DAG). Diacylglycerol is then transformed into triglycerides (TG) and very low-density lipoprotein (VLDL), which can lead to insulin resistance or decreased insulin sensitivity.[44]

Additionally, DAG can activate novel-CCP, leading to a reduction in phosphorylated tyrosine from the *Insulin Receptor Substrate* (IRS), which contributes to insulin resistance. Excess fructose in the body disrupts metabolism and the uptake of glucose into tissues, as fructose is more commonly metabolized into fat rather than glycogen, thereby promoting insulin resistance.[45,46]

Nitric oxide (NO) is produced by endothelial cells in the walls of blood vessels. It causes relaxation in smooth muscles, leading to the widening of blood vessels. This function helps to maintain stable blood pressure in mice and can prevent hypertension and cardiovascular diseases.[52]

Additionally, NO plays a role in reducing inflammation. When levels of NO in the body are adequate, it contributes positively to these health outcomes. When nitric oxide (NO) levels in the body are high, it indicates that endothelial function is healthy, which helps maintain stable blood pressure. Conversely, low NO levels can signify oxidative stress or inflammation, potentially leading to acute and even chronic inflammatory responses. Therefore, NO levels can also serve as a marker for inflammatory or oxidative status in animal models.[47]

Under normal conditions, mice produce malondialdehyde (MDA) as a result of lipid peroxidation, which is part of normal metabolism. Although MDA levels serve as a marker of oxidative stress, they are typically kept low due to effective detoxification and excretion mechanisms. Lipid peroxidation occurs when free radicals form and propagate, attacking unsaturated fatty acids in cell membranes. This process leads to the production of MDA, which can damage cell membranes and trigger an inflammatory response. Additionally, kencur rhizome extract contains active compounds that may play a role in mitigating these effects.[48] Kencur rhizome extract contains active compounds like flavonoids and kaempferol, which are known for their strong antioxidant properties. These compounds help neutralize free radicals and reduce lipid peroxidation.[22]

Endothelial cell damage occurs due to the increased formation of superoxide free radicals. These radicals can lead to the oxidation of low-density lipoprotein (LDL), resulting in the formation of hydroxyl groups in endothelial cells and the smooth muscle of blood vessels. This process is associated with elevated levels of malondialdehyde in the blood. Additionally, these hydroxyl radicals react with *polyunsaturated fatty acids*, which are abundant in cell membranes. This reaction can lead to peroxidation, producing lipid peroxides.[49]

Kaempferia galanga shows promising potential in addressing endothelial dysfunction, a key factor in cardiovascular disease. Its primary mechanism of action involves antioxidant and anti-inflammatory properties, which help reduce oxidative stress and improve endothelial function. Research indicates that *Kaempferia galanga* extract contains various bioactive compounds, including flavonoids and phenols, that contribute to scavenging free radicals, minimizing cell damage, and providing protective benefits.[50]

Previous research indicates that methanol extracts from *Kaempferia galanga* possess significant radical scavenging activity, which is closely linked to its antioxidant properties. In the context of endothelial dysfunction, this compound may enhance blood vessel relaxation by increasing the bioavailability of nitric oxide (NO). This is crucial for maintaining the elasticity and proper functioning of blood vessels.[51]

Based on the results of the ERK 50 and ERK 100 experiments, it has been demonstrated that ERK 50 effectively lowers blood glucose levels and prevents the formation of foam and inflammatory cells. In contrast, ERK 100 shows optimal results in suppressing increases in body weight, triglyceride levels, and MDA levels, while also enhancing nitric oxide (NO) levels. Therefore, ERK 100 holds greater potential for controlling metabolic and inflammatory parameters.

5. Conclusion

The research findings suggest that extract derived from kencur rhizome (*Kaempferia galanga* L.) exhibits potential in ameliorating metabolic disturbances. The study revealed a reduction in malondialdehyde (MDA) concentrations and an elevation in nitric oxide (NO) levels. These results point to the possibility of utilizing kencur rhizome extract as a therapeutic intervention for metabolic syndrome, primarily due to its apparent ability to alleviate inflammation and oxidative stress.

Conflict of Interest

The authors declare that they have no conflicts of interest related to this work.

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