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Antihypertensive Jamu Supplementation Improves Blood Pressure and Renal Oxidative Stress Markers in Fructose-Fed Rats

Suplementasi Jamu Antihipertensi Menurunkan Tekanan Darah dan Memperbaiki Marka Stres Oksidatif Ginjal pada Tikus yang Diinduksi Fruktosa

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ABSTRACT

High fructose consumption induces hypertension and renal oxidative stress, and herbal supplements (jamu) are potential agents for reversing this damage. This study examined the antihypertensive and antioxidant activity of a jamu formulation by measuring blood pressure and renal superoxide dismutase (SOD), glutathione (GSH), and malondialdehyde (MDA) levels in fructose-induced rats. Thirty Sprague-Dawley rats were divided into six groups: jamu at 0.01 (A1), 0.02 (A2), and 0.03 g/kg body weight (BW) (A3); captopril as the positive control (PC); negative control (NC); and normal control (SC). Rats received 10% fructose for 8 weeks to induce hypertension, continuing concurrently during the 2-week treatment period (weeks 9–10). Jamu supplementation significantly reduced blood pressure and MDA levels and increased SOD activity and GSH levels compared with the NC group ($p < 0.05$). Two weeks of jamu administration exerted antihypertensive and antioxidant effects, improving blood pressure control and renal oxidative stress markers in fructose-fed rats.

ABSTRAK

Konsumsi fruktosa yang tinggi memicu hipertensi dan stres oksidatif pada ginjal. Jamu antihipertensi berpotensi memulihkan kondisi tersebut. Penelitian ini bertujuan menilai aktivitas antihipertensi dan antioksidan jamu tersebut dengan mengukur kadar superoksida dismutase (SOD), glutation (GSH), dan malondialdehida (MDA) pada ginjal tikus yang diinduksi fruktosa 10%. Tiga puluh ekor tikus Sprague-Dawley dibagi menjadi enam kelompok: jamu dosis 0,01 (A1), 0,02 (A2), dan 0,03 g/kg berat badan (BB) (A3); kaptopril sebagai kontrol positif (PC); kontrol negatif (NC); dan kontrol normal (SC). Tikus diinduksi dengan fruktosa 10% selama delapan minggu, dilanjutkan bersamaan selama periode perlakuan 2 minggu (minggu ke-9 dan ke-10). Pemberian jamu secara signifikan menurunkan tekanan darah dan kadar MDA serta meningkatkan aktivitas SOD dan kadar GSH dibandingkan dengan NC ($p < 0,05$). Pemberian jamu selama dua minggu memberikan efek antihipertensi dan antioksidan, memperbaiki kontrol tekanan darah dan marka stres oksidatif ginjal pada tikus yang diinduksi fruktosa.

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1. INTRODUCTION

Metabolic syndrome (MS) is a collection of metabolic disorders associated with an increased risk of diabetes mellitus and cardiovascular disease. Risk factors that support the occurrence of metabolic syndrome are hypertension, dyslipidemia, and obesity. The criteria for metabolic syndrome across several health organizations differ slightly, requiring that 3 of 5 criteria be met for diagnosis (Nilsson et al., 2019). Generally, the cause of the metabolic syndrome is an unhealthy diet and lifestyle, such as consuming fast food or consuming foods high in fat, sugar, and salt, which can be a significant risk factor for metabolic syndrome. Around 20-25% of adults in the world experience metabolic syndrome; in Indonesia alone, the prevalence of metabolic syndrome occurs as much as 39.0%, which is based on sex, there are 28.0% and 46.2% in Indonesian men and women, respectively (Sigit et al., 2020). Fructose is one of the triggers for obesity, hypertension, and kidney disease. Fructose that enters the body is converted to glucose in the kidneys. Renal glucose release increased by 360% in rats and 300% in humans during diabetic conditions compared to non-diabetic states. Glucose and fructose can generate reactive oxygen species (ROS) via mitochondrial oxidation, the nicotinamide adenine dinucleotide phosphate (NADPH) pathway, and the insulin pathway (Lee & Jose, 2021). Fructose intake can increase renin, angiotensin I, and angiotensin II activity in the kidneys, increase angiotensinogen levels in the liver, and increase ACE activity in the lungs (Kim et al., 2020). High-fructose feeding quickly causes metabolic syndrome and hyperinsulinemia in animal models (L. Hidayati et al., 2020). Despite equivalent increases in body weight and adiposity, hyperinsulinemia is more pronounced in rodent models fed high-fructose than in those fed high-dextrose. Similarly, feeding humans a high-calorie fructose diet raises their blood insulin levels. Insulin resistance in certain combinations of liver, muscle, and adipose tissue can cause fructose-induced hyperinsulinemia, a condition often used as a proxy for insulin resistance (Hannou et al., 2018).

There is a close relationship between metabolic syndrome and chronic kidney disease. Renal damage from metabolic syndrome is characterized by decreased glomerular filtration rate, proteinuria with or without microalbuminuria, tubular atrophy, and interstitial fibrosis. The etiological factor in chronic kidney disease associated with metabolic syndrome is insulin resistance, which leads to oxidative stress, inflammation, and renal insufficiency (Prasad, 2014). Kidneys are organs that play a role in homeostasis, maintain fluid and electrolyte balance, and produce renin, which helps regulate blood pressure. Kidneys are the main organs of excretion, with high rates of oxidative metabolism and high energy requirements. The proximal tubular cells in the kidney reabsorb essential nutrients after glomerular filtration. The kidneys are susceptible to oxidative stress damage (Kitada et al., 2020). Oxidative stress in the kidney results from increased ROS generated by pro-oxidant enzymes and a concomitant decrease in antioxidants. This increase in ROS causes kidney fibrosis and inflammation, resulting in significant tissue damage, accompanied by increased lipid peroxidation, DNA damage, protein modifications, and mitochondrial dysfunction (Lee & Jose, 2021). The most widely used markers of oxidative stress are malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH). Free radicals can attack or steal electrons from other molecules, thereby generating additional free radicals that can damage cells (Phaniendra et al., 2015). The body responds to excessive free radical formation by producing SOD. SOD is an antioxidant enzyme that can prevent cell damage by converting superoxide anions into less harmful components, namely hydrogen peroxide. Glutathione (GSH) is an essential antioxidant for microorganisms because it helps protect against ROS-induced cell damage, including lipid peroxides, free radicals, and heavy metals. GSH can bind ROS via enzymatic and non-enzymatic reactions; in addition, GSH can protect cells from damage caused by reactive nitrogen species (Jomova et al., 2024).

Jamu is a traditional herbal medicine in Indonesia that has long been used for health maintenance and the prevention and management of various health conditions. Indonesian people use herbal medicine to treat their illnesses, one of which is hypertension. Research shows that 49.53% of Indonesians use herbal medicine for health maintenance and treatment, with 95.6% of those who consume jamu reporting benefits (Andriati & Wahjudi, 2016). This study used antihypertensive jamu with plant constituents, namely *Phaleria macrocarpa* fructus, *Gynura procumbens* leaves, *Imperata cylindrica* radix (alang-alang), *Centella asiatica* herb, and *Syzygium polyanthum* folium.

The antihypertensive jamu formulation investigated in this study has previously undergone standardization and phytochemical characterization, providing information on its constituent profile and chemical consistency. However, it has not yet been empirically established whether this jamu formulation exhibits measurable antihypertensive effects and can ameliorate renal oxidative stress in vivo under conditions of chronic metabolic stress induced by fructose. Therefore, evaluating the efficacy of the standardized antihypertensive jamu formulation using a fructose-fed rat model is necessary to determine whether the previously established standardization translates into measurable biological activity in vivo. This study provides scientific evidence on the effects of the antihypertensive jamu formulation at different doses on blood pressure and renal oxidative stress parameters, including malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD), with captopril serving as a positive control. This approach enables the evaluation of the relationship between dose and biological response while distinguishing the effects of the jamu formulation from fructose-induced changes and normal physiological conditions. The present study specifically focuses on blood pressure regulation and renal oxidative stress and does not aim to demonstrate direct effects on renal function, cardiovascular tissue protection, angiotensin-converting enzyme (ACE) activity, or the renin–angiotensin–aldosterone system (RAAS), as these parameters were not directly measured in the

present study. Accordingly, the objective of this study was to evaluate the antihypertensive effects and the effects on renal oxidative stress of a standardized jamu antihypertensive formulation in fructose-fed rats. We hypothesized that administration of the standardized antihypertensive jamu formulation would attenuate fructose-induced increases in blood pressure and ameliorate renal oxidative stress, as indicated by a dose-dependent reduction in MDA levels and improvements in endogenous antioxidant parameters, particularly GSH and SOD.

2. METHODS

2.1. Instruments and material

The antihypertensive jamu utilized in this study was acquired as commercial capsules with a standardized fill weight of 0.54 g per capsule. The product was manufactured by PT Mahkota Dewa Indonesia, Jakarta, Indonesia (POM TR063361861). The specific formulation consists of an optimized combination of five verified Indonesian medicinal plants: *P. macrocarpa* fruits, *G. procumbens* leaves, *I. cylindrica* roots, *C. asiatica* herbs, and *S. polyanthum* leaves. The comprehensive chemical standardization, including non-specific and specific parameters, has been established and fully described in our previous work (Eff et al., 2020). Sprague-Dawley rats (age: 8–10 weeks, initial body-weight range: 180–220 g) were obtained from the National Agency of Drug and Food Control, Jakarta, Indonesia. Captopril tablets (25 mg/tablet, pharmaceutical grade, certified by the Indonesian Food and Drug Authority [Badan POM]; PT Dexa Medica, Palembang, Indonesia), Physiological NaCl pH 7.4 (analytical grade; Merck KGaA, Darmstadt, Germany), PBS solution (Merck KGaA, Darmstadt, Germany), trichloroacetic acid (TCA, ≥99 purity/analytical grade; Merck KGaA, Darmstadt, Germany), thiobarbituric acid (TBA, ≥98 purity/analytical grade; Merck KGaA, Darmstadt, Germany), Superoxide Dismutase assay kit (Ransod® Kit, diagnostic reagent grade; Randox Laboratories Ltd., Crumlin, County Antrim, UK), 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB, ≥98 purity/analytical grade; Sigma-Aldrich, St. Louis, MO, USA), and sodium pentobarbital (Kimia Farma), D-fructose (≥ 99% purity, analytical grade; Merck KGaA, Darmstadt, Germany), Rat Surgical Kit (Kent Scientific Corp., Torrington, CT, USA), beaker glass (Pyrex® Low Form; Corning Inc. [Pyrex Germany], Mainhausen, Germany), drinking bottle (Lixit® Animal Care Products, Napa, CA, USA), stirring rod (Pyrex® Series; Corning Inc. [Pyrex Germany], Mainhausen, Germany), centrifuge (Eppendorf SE, Hamburg, Germany), freezer temperature -20°C (Thermo Fisher Scientific, Waltham, MA, USA), rat cage (individually Ventilated Cages; Orchid Scientific, Nashik, India), digital balance (Quintix® Series; Sartorius AG, Göttingen, Germany), **non-invasive** blood pressure (Model 229; IITC Life Science Inc., Woodland Hills, CA, USA), mouse restrainer (IITC Life Science Inc., Woodland Hills, CA, USA), UV spectrophotometer (Genesys™ 10S; Thermo Fisher Scientific, Waltham, MA, USA), Eppendorf tube (Safe-Lock, 1.5 mL; Sartorius AG, Göttingen, Germany), vortex mixer (Maxi Mix II; Thermo Fisher Scientific, Waltham, MA, USA).

2.2. Making jamu solution

Jamu was stored in airtight containers at room temperature (25 ± 2°C) away from direct sunlight. The instructions on the package stated that it might be used to lower blood pressure. Instructions for using jamu: take 1 capsule twice a day. Jamu was removed from the capsules, brewed with hot water to a total volume of roughly 100 ml, and taken in two doses on the same day, according to the directions on the reverse side of the packaging. Storage was recommended in a dry place. Experimental dosages for rat experiments were selected based on the packet content of 0,54 g per human being. The dose conversion from human to rat was calculated using the standard body-surface-area (BSA) conversion method by Laurence and Bacharach. Based on the human daily dose of 1.08 g/day (one 0.54 g capsule taken twice daily) for a 60 kg individual, the equivalent dose for a 200 g rat was calculated as 0.01944 g per rat, or approximately 0.097 g/kg body weight (BW). Experimental doses were selected at lower fractions of 0.01, 0.02, and 0.03 g/kg BW to examine graded therapeutic outcomes. To prepare the solution, the capsule contents were dissolved in distilled water at 80°C and stirred continuously for 15 minutes. The mixture was allowed to cool to room temperature (25 ± 2°C) and filtered through Whatman No. 1 filter paper to achieve the final concentrations. The prepared jamu was administered twice daily via oral gavage in a standardized volume of 1.0 mL per rat. The absolute amount administered was calculated and adjusted weekly for each animal based on its changing body weight (Afroz et al., 2014).

2.3. Animals and Experimental Housing

Thirty male Sprague-Dawley rats (age: 8–10 weeks, initial body-weight range: 180–220 g) were acclimated to the laboratory environment for 7 days before any experimental manipulation. The animals were housed in standard polycarbonate cages with 3 rats per cage under strictly controlled environmental conditions: temperature maintained at 22 ± 2°C, relative humidity at 50–60%, and an automated 12-hour light/dark cycle (lights on at 07:00 AM). The cages were clean and provided with sterilized wood shavings as bedding and paper shreds for environmental enrichment. Rats had unrestricted ad libitum access to standard commercial rodent pellet food and fresh drinking water. Animal health, behavior, and physiological signs of distress were monitored daily by trained laboratory staff.

The rats were randomly allocated into six experimental groups (n = 5 per group) using a simple randomization sequence generated by a computer random-number program. The exclusion criteria during the study were defined as severe physical injury, weight loss exceeding 20% of baseline, or failure to induce a hypertensive state after 8 weeks (no rats met these criteria). Humane endpoints were established according to institutional animal ethics guidelines, requiring immediate euthanasia via an overdose of anesthesia if animals displayed persistent signs of severe pain,

lethargy, or inability to access food or water; however, no animals reached these humane endpoints during the 10-week experimental timeline. The Universitas Esa Unggul health research ethics committee approved this study, with approval number 0161-20.152/DPKEKEP/FINAL-ENUEUN/2020, dated 30 May 2020.

2.4. Treatment and group division

Thirty previously acclimatized rats were divided into six groups. The groups are as follows: jamu at 0,01 g/kg BW (A1), 0,02gr g/kg BW (A2), 0,03g/kg BW (A3), captopril as a positive control (PC) at 0.0005 g/kg BW, negative control (NC), and normal control (SC). Treatment and groups division details are in **Table 1**.

All groups received a 10% fructose solution for 8 weeks to induce hypertension, except group SC, and its administration continued concurrently during the 2-week treatment period (Weeks 9 and 10) to maintain a sustained hypertensive environment. For the induction of hypertension, analytical-grade D-fructose Merck) was dissolved in distilled water to prepare a 10% (w/v) solution. This solution was provided to the designated groups ad libitum as their sole drinking source. To maintain hygiene and consistency in concentration, drinking bottles were washed and refilled with a new solution daily. The average daily fluid intake was recorded at approximately 32 ± 3 mL per rat. The Experimental Group Design Matrix is presented in **Table 1**. Blood pressure and body weight were measured once a week. At the end of the 8-week induction phase, baseline hemodynamic monitoring was performed using non-invasive tail-cuff plethysmography (IITC Life Science®) to confirm successful model establishment. Animals in the fructose-fed groups showed a significant increase in systolic blood pressure compared with the normal control group ($p < 0.05$), thereby confirming successful induction of hypertension prior to the administration of jamu or captopril therapies. The rats were anesthetized with sodium pentobarbital at a 50 mg/kg BW dose, sacrificed, and the kidneys were removed at the beginning of the 11th week. PBS solution (pH 7.4) was used to homogenize the kidneys, which were then vortexed and centrifuged at 3000 rpm for 10 minutes. Before measuring SOD activity, GSH levels, and MDA levels, the supernatant was separated and stored at -20°C.

Table 1. Experimental Group Design Matrix

Group Label	N	Fructose exposure (weeks 1- 10)	Treatment administered (weeks 9-10)	Treatment Duration (weeks)
Normal control (SC)	5	None (standard drinking water	Distilled Water	2
Negatif control (NC)	5	10% Fructose Solution ad libitum	Distilled Water	2
Positive control (PC)	5	10% Fructose Solution ad libitum	Captopril 0.0005 g/kg BW	2
Jamu dose 1 (A1)	5	10% Fructose Solution ad libitum	Antihypertensive Jamu 0.01 g/BW	2
Jamu dose 2 (A2)	5	10% Fructose Solution ad libitum	Antihypertensive Jamu 0.02 g/BW	2
Jamu dose 3 (A3)	5	10% Fructose Solution ad libitum	Antihypertensive Jamu0.03 g/BW	2

2.5. Blood pressure measurement

We monitored the rats' hemodynamic changes using a non-invasive tail-cuff plethysmography system (IITC Life Science®), taking careful steps to ensure the animals remained calm and comfortable. To reduce stress and prevent sudden blood pressure spikes caused by fear, every rat completed a gentle 3-day training session before we recorded any formal baseline data. This helped them get used to the physical restrainer and the gentle pressure of the cuff inflation. We conducted all measurement sessions strictly in the morning between 09:00 AM and 12:00 PM to respect the animals' natural circadian rhythms and ensure consistency. During each session, we ran 10 consecutive pressure cycles; we routinely set aside the first 3 cycles to allow the rats to stabilize, using the average of the remaining 7 cycles as our definitive reading. We accepted these readings only when they were highly stable, marked by a standard deviation of less than 10 mmHg. Throughout the study, we consistently recorded systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). Finally, to preserve strict objectivity and protect the integrity of the data, the laboratory technician operating the equipment was kept completely unaware of which treatment group each rat belonged to.

2.6. Kidney Tissue Isolation and Homogenization

Following humane euthanasia, the left kidney from each rat was carefully harvested, cleared of surrounding fatty capsule remnants, and washed thoroughly in ice-cold saline. A standardized section of the renal cortex (approximately 400–500 mg of wet tissue weight) was precisely weighed and placed in ice-cold 0.1 M Phosphate Buffered Saline (PBS, pH 7.4) at a strict 1:10 (w/v) tissue-to-buffer ratio (100 mg tissue per 1.0 mL buffer). To preserve molecular integrity, the tissue was finely chopped and homogenized using a mechanical homogenizer while continuously immersed in ice. The resulting crude homogenate was centrifuged at 10,000 × g for 15 minutes at 4°C to pellet cellular debris. The clear supernatant was immediately separated, aliquoted into multiple small microcentrifuge tubes to ensure a single freeze-thaw cycle, and stored in an ultra-low-temperature freezer at -80°C for up to 2 months prior to biochemical analysis. Because a total protein concentration assay was not performed, all downstream biochemical marker levels (MDA, SOD, and GSH) were systematically normalized and calculated based on the precise wet tissue weight (expressed as units or content per gram of tissue) (Afsar et al., 2020).

2.7. SOD Activity Evaluation

We evaluated superoxide dismutase (SOD) activity in kidney tissue samples using a commercial Ransod kit (Randox Laboratories Ltd., Crumlin, UK). To perform the assay, 50 µL of the prepared kidney tissue supernatant was mixed with the kit's substrate reagent (containing xanthine and INT) and xanthine oxidase enzyme solution according to the manufacturer's instructions. The reaction mixture was incubated, and the absorbance was measured at 505 nm using a Genesys spectrophotometer. We recorded the initial absorbance (A_1) exactly 30 seconds after the reaction was initiated and the final absorbance (A_2) after 3 minutes. A standard calibration curve was constructed using pure SOD standard solutions from the kit to determine the enzyme's inhibitory capacity. A reagent blank (distilled water instead of the tissue sample) was run simultaneously for blank correction and to establish the baseline for uninhibited chromogen formation. One unit (U) of SOD activity was defined as the amount of enzyme required to inhibit the rate of INT reduction by 50% under the assay conditions. The percentage of inhibition for each sample was calculated using the following equation:

$$\text{Percent Inhibition (\%)} = \frac{\Delta \text{ A blank} - \Delta \text{ A sample}}{\Delta \text{ A blank}} \times 100$$

All measurements were strictly performed in triplicate to ensure technical reproducibility. Because total protein concentration was not evaluated in this study, the final calculated SOD activity was normalized directly against the initial sample dilution factor and the precise wet weight of the kidney tissue, with the final values reported as Units per gram of tissue (Prijanti & Hawali, 2018).

2.8. Measuring GSH Levels

To initiate the assay, 50 µL of the kidney homogenate was thoroughly mixed with 200 µL of 5% trichloroacetic acid (TCA) and vortexed to precipitate the proteins. Following centrifugation to isolate the cellular debris, a fraction of the clear supernatant was collected. We then added 25 µL of 10 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) and 1750 µL of 0.1 M phosphate buffer (pH 7.4). The reaction mixture was incubated calmly at room temperature for 1 hour. During this period, the sulfhydryl groups of GSH reacted with DTNB to produce a vibrant yellow-colored compound, 5′-thio-2-nitrobenzoic acid (TNB). The final absorbance was measured at 412 nm using a spectrophotometer. To ensure rigorous technical reproducibility, all samples were analyzed in triplicate and corrected against a reagent blank, in which the tissue sample was replaced with distilled water. The absolute concentrations were calculated using a linear calibration equation derived from a standard curve of pure glutathione solutions (0 - 100µg/mL). Because total protein concentration was not evaluated in this study, the final GSH content was systematically normalized to the wet tissue mass and expressed as nanomoles per gram of tissue (nmol/g tissue) (Abarikwu et al., 2017).

2.9. Measuring MDA Level

We quantified lipid peroxidation in the renal tissue by measuring Malondialdehyde (MDA) levels using a modified Thiobarbituric Acid Reactive Substances (TBARS) assay. Briefly, approximately 200 mg of kidney tissue homogenate was mixed with 180 µL distilled water and 1 mL 20% trichloroacetic acid (TCA). The mixture was thoroughly vortexed and centrifuged at 3000 rpm for 10 minutes to separate the precipitated proteins and isolate the clear supernatant. Next, we collected the supernatant and added 2 mL of 0.67% thiobarbituric acid (TBA) reagent. The mixture was vortexed again and heated in a boiling water bath at 100^{0}C for 10 minutes to induce the formation of the pink-colored MDA-TBA chromophore. After the reaction tubes were cooled to room temperature under running tap water, the absorbance of the solution was measured at 530 nm using a spectrophotometer. To maintain high experimental rigor, all measurements were conducted in triplicate and corrected for a reagent blank prepared with distilled water rather than tissue homogenate. The absolute concentrations were calculated using a linear calibration equation derived from a standard MDA curve prepared with 1,1,3,3-tetramethoxypropane (TMP). The final MDA content was normalized to the initial wet tissue mass and expressed as nanomoles per gram of tissue (nmol/g tissue) (Abarikwu et al., 2017).

2.10. Data analysis

Statistical analyses were performed using IBM SPSS Statistics software (Version 22.0; IBM Corp., Armonk, NY, USA). Normality and homogeneity of variance were assessed using the Shapiro-Wilk and Levene's tests, respectively. For biochemical markers (SOD, GSH, MDA), differences between groups were analyzed using one-way ANOVA, followed by Tukey's post hoc test. For body weight and blood pressure parameters monitored over time, a two-way repeated-measures ANOVA was employed.

3. RESULTS AND DISCUSSION

3.1. Body weight

Changes in mean body weight (g) across experimental groups during 10 weeks of fructose dietary load and during weeks 9–10 of the Jamu intervention are presented in **Figure 1**. The two-way repeated-measures ANOVA revealed a statistically significant time-dependent effect on body weight progression across all experimental groups. The statistical analysis revealed a highly significant main effect of time on body weight progression ($p = 0.000$), demonstrating the expected physiological growth over the course of the study. A significant interaction effect between time and treatment groups was also observed ($p = 0.000$), establishing that the specific interventions distinctly modulated the rate and pattern of weight gain. At baseline (Week 1), the mean body weight across all cohorts was 209.5 ± 5.7 g. The normal control group (SC) exhibited a standard physiological growth pattern, rising from 210.0 g at Week 1 to 248.0 g at Week 2, fluctuating between 241.0 and 269.0 g through Week 5, and stabilizing

around 244.0–248.0 g from Week 6 through the conclusion of the study (248.0 g at Week 10). In contrast, the untreated negative control group (NC) reached a premature weight peak of 270.0 g, sustained from Week 6 through Week 9, then declined to 261.0 g during the second week of treatment. This reduction indicates metabolic stress or progressive pathology induced by the disease model. Among the jamu-treated cohorts, the weight response diverged by dose during the treatment phase. The lowest-dose group (A1) showed continuous weight gain through Week 10, reaching 290.0 g and modestly exceeding the standard captopril group (PC; 277.0 g), whereas the mid- and high-dose groups plateaued earlier and ended the study below PC: A2 peaked at 277.0 g at Week 8 before declining to 264.0 g by Week 10, and A3 plateaued at 264.0 g from Week 9 onward. Despite this dose-dependent difference in the extent of weight gain, all three jamu-treated groups showed substantial increases from baseline, consistent with an absence of overt toxicity under these conditions.

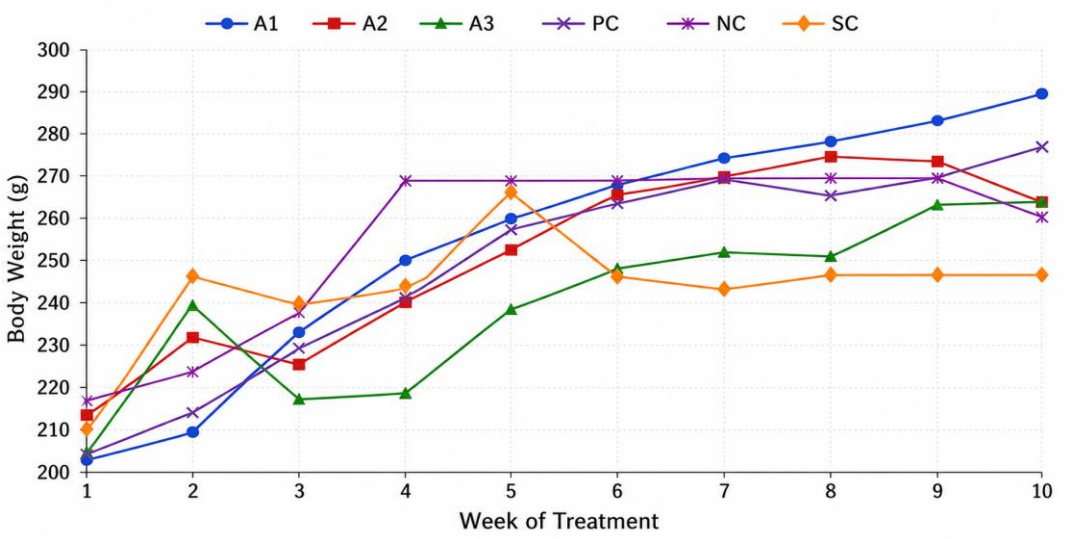

Figure 1. Changes in mean body weight (g) across experimental groups during 10 weeks of fructose dietary load and weeks 9–10 of Jamu intervention. SC, normal control (fructose-free); NC, negative control (10% fructose, untreated); PC, positive control (10% fructose + captopril 0.0005 g/kg BW); A1, A2, A3, 10% fructose + antihypertensive jamu at 0.01, 0.02, and 0.03 g/kg BW, respectively. Data are presented as mean values (n = 5 rats per group).

From **Figure 1**, it can be seen that all rat groups showed a significant increase in body weight from week 1 to week 8. Group A1 had the highest percentage change in body weight among the groups, 38.23%. In addition, the average weekly increase is 4.78%. Excessive fructose consumption can, in the long term, increase plasma triglyceride levels and lead to obesity. Fructose and other carbohydrates are essential substrates for triglyceride synthesis, which is stored in the skin as fat when intake is excessive (Köseler et al., 2018). Additionally, excessive fructose consumption can lead to obesity, cardiovascular disease, and changes in lipid profiles (Pereira et al., 2017; Xie, 2017). A study by Kusumastuty et al. (2020) demonstrated that administering 30% fructose solution and a high-fat diet significantly altered the feeding behavior of rats. The high caloric intake from the liquid fructose suppressed the animals' appetite, thereby drastically decreasing the volume of standard feed consumed (6.31 ± 1.12 grams/day). Nonetheless, the energy from liquid fructose led to a high total daily caloric intake. In the present study, the amount of standard feed consumed by the experimental animals per day was not directly measured. Although the volume of solid food intake was not recorded, the metabolic effects of fructose administration were clearly evident in the negative control group from clinical manifestations and body weight changes (Kusumastuty et al., 2020). These results are similar to those of a study by Susilawati et al., which showed that oral administration of 60% fructose for 60 days in rats did not result in a significant difference in body weight between the normal and fructose groups. Nonetheless, the fructose-treated rat group showed enlargement of white adipose tissue, indicating accumulation of harmful visceral fat due to fructose conversion in the liver to glycerol-3-phosphate (lipogenesis), as well as shrinkage of brown adipose tissue, which generates body heat (thermogenesis) and burns calories. This shrinkage subsequently reduces the body's capacity to burn energy (Susilawati et al., 2024).

3.2. Blood pressure regulation

Progression of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in fructose-fed rats over a 10-week observational period is shown in **Figure 2**. Statistical analysis utilizing a two-way repeated-measures ANOVA revealed a highly significant main effect of time on both systolic blood pressure (SBP; Wilks' Lambda = 0.109, F (9, 16) = 14.547, $p < 0.001$) and diastolic blood pressure (DBP; Wilks' Lambda = 0.147, F(9, 16) = 10.323, $p < 0.001$) progressions. This indicates substantial time-dependent physiological alterations over the 10-week experimental course. A statistically significant time-by-treatment interaction effect was also observed for both SBP (Wilks' Lambda = 0.014, F (45, 74.675) = 2.667, $p < 0.001$) and DBP (Wilks' Lambda = 0.028, F (45, 74.675) = 2.039, $p = 0.003$). This finding confirms that blood pressure regulation was modulated by the specific

interventions administered. The divergence in SBP and DBP profiles following the intervention period indicates the efficacy of the Jamu formulations (A1, A2, and A3) in modifying or stabilizing blood pressure parameters relative to both the standard drug control (PC) and the negative control (NC). From **Figure 2**, it can be seen that blood pressure increased significantly until the eighth week after 10% fructose was given. Blood pressure began to rise at week 3 of fructose administration. The groups that increased were the jamu group (doses 1, 2, and 3), the captopril control group, and the negative control group. Giving treatment for 2 weeks, from week 9 to week 10, decreased blood pressure in the jamu group at doses 1, 2, and 3, and in the captopril control group. The reduction in systolic and diastolic blood pressure was significantly greater than in the negative control (0.001; $p < 0.05$). Among the treatment groups, the jamu group at a dose of 0.02 g/kg BW showed the greatest percentage reductions in systolic and diastolic blood pressure from the post-induction baseline, at 18.00% and 13.24%, respectively. A large-scale meta-analysis conducted by Arya et al. (2025) on the induction of hypertension and metabolic syndrome demonstrated that fructose consumption significantly increased systolic blood pressure (SBP) in rats by an average of 31.05 mmHg ($p < 0.01$). This phenomenon of elevated SBP and DBP with a high-fructose diet aligns with the physiological changes observed in the negative control (NC) group without treatment, which progress over time. Furthermore, the study by Arya et al. (2025) reported that the administration of either 10–30% w/v or 60–75% w/v fructose consistently triggered hypertension across all exposure durations, including <8 weeks, 8 weeks, and >8 weeks (Arya et al., 2025). In our study, the administration of jamu at doses of 0.01, 0.02, and 0.03 g/kg BW (A1, A2, and A3) demonstrated therapeutic efficacy in inhibiting the progression of elevated blood pressure. According to the mechanistic review by Arya et al. (2025), metabolic hypertension is generally driven by several pathways, including increased oxidative stress, triggering of inflammatory responses (NLRP3 inflammasome activation), and hyperuricemia and endothelial dysfunction (Arya et al., 2025). Fructose elevates blood pressure by triggering early endothelial dysfunction, which develops concurrently with increases in SBP and DBP. This impairment is primarily driven by the failure of local vascular relaxation mechanisms due to disruption of $K_{Ca}3.1$ ion channels within the EDH pathway (Hamad & Özkan, 2024). The administered jamu A1, A2, and A3 are hypothesized to modulate one or more of these pathways. Their ability to modulate SBP and DBP profiles indicates that the bioactive compounds in these jamu do not merely act as nonspecific symptom stabilizers but rather function as effective cardiovascular protective agents. The success of these herbal formulations in maintaining or improving blood pressure parameters to levels approaching those of the positive control (PC) drug indicates that these traditional formulations have scientific potential as alternative or complementary antihypertensive therapies, particularly for minimizing the long-term risk of cardiovascular dysfunction induced by metabolic disorders.

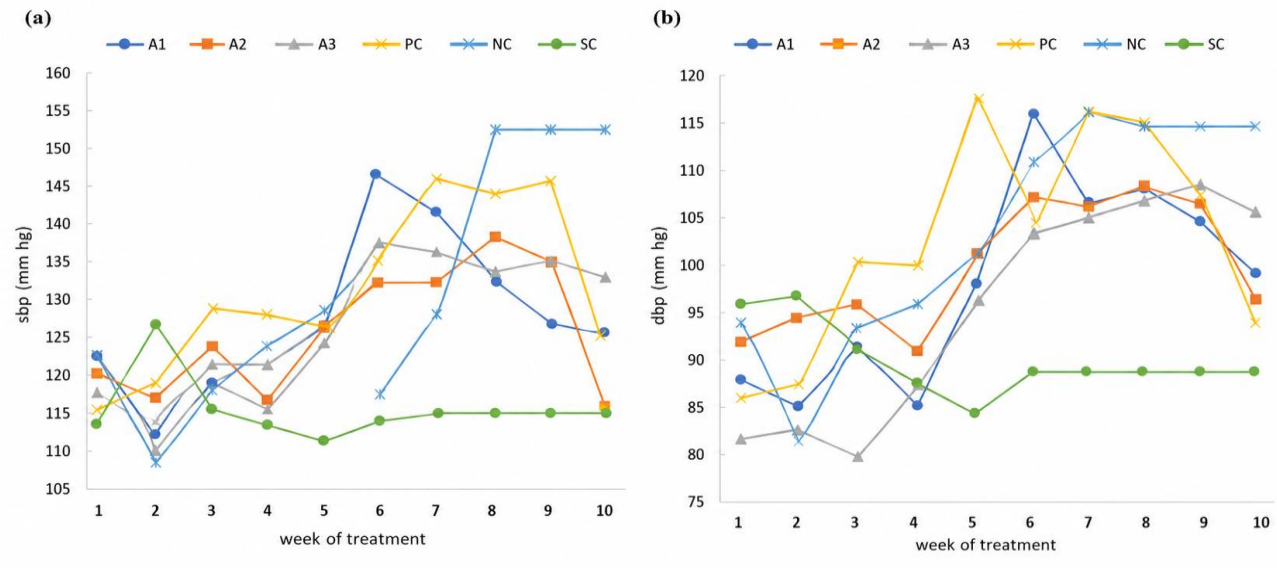

Figure 2. Effects of Jamu formulations on time-dependent blood pressure alterations in fructose-induced hypertensive rats

Mean of systolic blood pressure (SBP) expressed in millimeters of mercury (mmHg); and (B) Mean of diastolic blood pressure (DBP) expressed in mmHg. Experimental animals (n = 5 rats per group) were randomly assigned to six distinct cohorts: Negative Control (NC, 10% w/v fructose-induced, untreated); Standard Control (SC, fructose-free, baseline reference); Positive Control (PC, captopril-treated at 0.0005 g/kg BW); and three intervention groups receiving varying Jamu formulations designated as A1 (0.01 g/kg BW), A2 (0.02 g/kg BW), and A3 (0.03 g/kg BW); each administered orally. All data points are presented as Mean ± Standard Deviation (SD). Statistical significance was evaluated using a two-way Analysis of Variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons.

3.3. Renal oxidative stress markers (MDA, GSH, SOD)

Table 2 presents oxidative stress parameters, including malondialdehyde (MDA), glutathione (GSH), and superoxide dismutase (SOD) levels, across six groups. This study aimed to

evaluate the efficacy of varying herbal medicine (jamu) doses at 0.01, 0.02, and 0.03 g/kg BW (A1, A2, and A3, respectively) in comparison with the normal control (SC), negative control (NC), and positive control (PC) groups.

Table 2. Renal MDA, GSH, and SOD levels in fructose-fed rats after treatment

No	Group	N	Mean ± SD		
			MDA (nmol/g tissue)	GSH (nmol/g tissue)	SOD (U/g tissue)
1	SC	5	3.064 ± 0.116	0.506 ± 0.065	215.545 ± 10.544
2	NC	5	9.797 ± 1.727	0.197 ± 0.013	88.099 ± 6.433
3	PC	5	3.396 ± 0.449**	0.433 ± 0.038*,**	218.226 ± 24.880*,**
4	A1	5	7.386 ± 0.387	0.298 ± 0.031**	151.912 ± 7.228
5	A2	5	5.915 ± 0.313	0.408 ± 0.020*	203.074 ± 10.383
6	A3	5	3.402 ± 0.262*,**	0.438 ± 0.026*,***	204.700 ± 7.26**

MDA, malondialdehyde; GSH, glutathione; SOD, superoxide dismutase. Data are presented as mean ± SD (n = 5 per group). Group differences were analyzed using one-way ANOVA followed by Tukey's post hoc test. *significantly different compared to the negative control (NC) ($p < 0.05$); ** not significant compared to normal control (SC) ($p > 0.05$)

Regarding MDA levels, the negative control (NC) group showed significantly higher levels (9.797 ± 1.727 nmol/g tissue) than the SC group (3.064 ± 0.116 nmol/g tissue), indicating that severe oxidative stress was successfully induced in the NC group. Conversely, the positive control (PC) group showed the lowest MDA levels (3.396 ± 0.449 nmol/g tissue), which did not differ significantly from the normal control (SC) group ($p = 0.981$). Within the treatment cohorts, the herbal preparation reduced MDA levels in a dose-dependent manner. Although the lowest dose in group A1 still maintained a relatively high MDA concentration (7.386 ± 0.387 nmol/g tissue), it was lower than that of the negative control (NC) group, but the difference was not significant ($p = 0.07$). The most optimal reduction in MDA levels was observed in the A3 group (3.402 ± 0.262 nmol/g tissue). Statistically, the MDA levels in the A3 group were significantly different from the NC group ($p = 0.00$) but showed no significant difference compared to the normal control (SC) group ($p = 0.98$).

Glutathione (GSH) is an endogenous, non-enzymatic antioxidant that plays a critical role in scavenging free radicals, and its reserves are typically depleted during oxidative stress (Novelli & Bianchetti, 2022). As shown in **Table 2**, GSH levels were sharply reduced in the negative control (NC) group (0.197 ± 0.013 nmol/g tissue) compared with the standard control (SC) group (0.506 ± 0.065 nmol/g tissue), confirming fructose-induced antioxidant depletion. Meanwhile, the Captopril (PC) group successfully maintained GSH levels at 0.433 ± 0.038 nmol/g tissue. In the treatment groups (A1, A2, and A3), gradual dose escalation restored GSH concentrations. The lowest herbal dose in group A1 did not significantly increase GSH compared with the normal control/SC group ($p = 0.254$). However, GSH levels in the A2 group (0.408 ± 0.020 nmol/g tissue) and A3 group (0.438 ± 0.026 nmol/g tissue) were significantly elevated compared to the NC group ($p = 0.00$). The GSH value in the A3 group was similar to those of both the positive and normal controls ($p = 0.995$), indicating that the herbal formulation at a dose of 0.03 g/kg BW (A3) is highly effective in preventing depletion or in restimulating endogenous GSH production.

Superoxide dismutase (SOD) serves as a first-line enzymatic antioxidant defense, catalyzing the conversion of superoxide radicals into hydrogen peroxide (Ighodaro & Akinloye, 2018). The lowest SOD activity was recorded in the NC group (88.099 ± 6.433 U/g tissue). In contrast, the PC group exhibited the highest SOD activity among all cohorts (218.226 ± 24.880 U/g tissue), which was significantly higher than that of the negative control (NC) but did not differ significantly from the normal control (SC) group. The upregulation of SOD activity was directly proportional to the increase in dosage. Groups A1 and A2 exhibited SOD activities of 151.912 ± 7.228 U/g tissue and 203.074 ± 10.383 U/g tissue, respectively. Group A3 demonstrated the highest SOD activity among the treated groups (204.700 ± 7.26 U/g tissue), showing no statistically significant difference from the normal control SC group ($p = 0.942$). Induction with 10% fructose for 10 weeks successfully established oxidative stress, characterized by a surge in MDA levels and a concomitant decline in GSH and SOD levels. Administration of the jamu at doses of 0.01, 0.02, and 0.03 g/kg BW exerted a dose-dependent protective antioxidant effect. Among the tested doses, group A3 was the most effective and optimal. The capacity of group A3 to suppress MDA levels and elevate GSH and SOD activities matched the efficacy of the positive control (PC) group, effectively restoring the oxidative stress parameter profiles to a state close to that of the normal control (SC) group. The findings of this study align with those of Yüksel et al. (2025), which demonstrated that high-fructose induction triggers oxidative stress by increasing lipid peroxidation (MDA) levels. However, our study showed a more pronounced depletion of endogenous antioxidants (GSH and SOD), which may be attributed to a longer fructose exposure duration (10 weeks) compared with the 30-day period in the study by Yüksel et al. Furthermore, the administration of the herbal preparation at a dose of 0.03 g/kg BW (A3) demonstrated a protective efficacy comparable to that of boric acid in restoring the body's oxidant-antioxidant balance (Yüksel et al., 2025). Our findings, which demonstrate that fructose induces oxidative stress, are supported by the study of Elsisy et al. (2021). They stated that a high-fructose diet serves as a highly effective model for inducing rapid and severe organ damage, which subsequently triggers inflammation

and cellular dysfunction. Furthermore, the manifestations of oxidative stress observed in our study—namely, the decline in GSH and SOD levels and the elevation of MDA—were influenced by the duration of fructose exposure (10 weeks). This aligns with the exposure-duration concept reported by Elsisy et al., in which longer exposure periods consistently result in significant biochemical damage (Elsisy et al., 2021). The molecular mechanism underlying the fructose-induced oxidative stress in our study can be elucidated based on the findings of Ai et al. (2025). They reported that excessive fructose consumption disrupts cellular metabolism, leading to hypoxanthine accumulation and a subsequent surge in reactive oxygen species (ROS) production. This metabolic pathway is directly responsible for the severe oxidative damage observed in the negative control (NC) group, which is characterized by elevated MDA levels and decreased GSH and SOD after 10 weeks of fructose exposure. The herbal preparation, particularly at the highest dose of 0.03 g/kg BW (A3), successfully restored the endogenous antioxidant equilibrium to a level comparable to that of the normal control (Ai et al., 2025).

3.4. Phytochemical basis of the jamu constituents

Antihypertensive herbal medicine (jamu) A consists of the following components: *Phaleria macrocarpa* fruits, *Gynura procumbens* leaves, *Imperata cylindrica* roots, *Centella asiatica* leaves, and *Syzygium polyanthum* leaves. *Phaleria macrocarpa*, also known as Mahkota dewa, is a medicinal plant native to Indonesia. Phalerin, gallic acid, Icaricide C, mangiferin, mahkoside A, dodecanoic acid, palmitic acid, desacetylflavicordin A, flavicordin A, flavicordin D, flavicordin A glucoside, ethyl stearate, lignans, alkaloids, and saponins are among the constituents isolated from *P. macrocarpa*. The fruit and leaves of *P. macrocarpa* have been found to contain flavonoids and phenolics, making them potent antioxidants. Gallic acid and 6-dihydroxy-4-methoxybenzophenone-2-O-D-glucoside, which has DPPH activity, are among the constituents found in the mesocarp, pericarp, and seed extract of *P. macrocarpa*. Fruit extracts of *P. macrocarpa* have been proven to enhance SOD levels (Alara et al., 2016; Altaf et al., 2013) and increase renal antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Yanti et al., 2014). According to a study by Rinayanti et al., leaf and fruit extracts exhibit ACE-inhibitory activity, with IC_{50} values of 189.13 ppm in petroleum ether, 157.74 ppm in ethyl acetate, and 101.52 ppm in methanol. Moreover, IC_{50} values in fruit are 161.7 ppm in petroleum ether and 139.11 ppm in ethyl acetate (Rinayanti et al., 2013).

Gynura procumbens (Lour.) is a tropical Asian medicinal plant found in China, Thailand, Indonesia, Malaysia, and Vietnam. It has traditionally been used in many countries to treat a wide range of health problems, including renal disease, rheumatism, constipation, diabetes, and high blood pressure (B. L. Tan et al., 2018). *G. procumbens* has chemical constituents such as flavonoids, saponins, tannins, terpenoids, and sterol glycosides found in the leaves. Furthermore, treatment with *G. procumbens extract resulted in a significant decrease in heart rate and strong negative chronotropic and negative inotropic effects in the right and left atria of rats*, respectively (Abrika et al., 2013). *G. procumbens* extracts have IC_{50} values of 431.54 ppm in petroleum ether, 227.41 ppm in ethyl acetate, and 452.69 ppm in methanol as ACE inhibitors (Rinayanti et al., 2013). *G. procumbens* has antioxidant properties, and the antioxidant effect was demonstrated by its inhibition of lipid peroxidation at a median effective concentration of 2.75mg/mL. *G. procumbens* appears to be a high-quality source of natural antioxidants. Most likely as a result of its high phenolic content (H. L. Tan et al., 2016).

Imperata cylindrica (L.) Beauv (Alang-alang) is a type of grass that grows continuously in the tropics and subtropics worldwide. Tannins, saponins, flavonoids, terpenoids, alkaloids, phenols, and cardiac glycosides have all been found in *I. cylindrica* leaf extract. On the other hand, the roots contain flavonoids, potassium, cylindrene, and graminone B (Liu et al., 2013). In NaCl-induced rats, a methanol extract of Alang-alang root exhibited antihypertensive activity. At tested doses of 60 and 90 mg/kg-BW, this extract substantially reduced the proportional amplitudes of stroke volume and heart rate, equivalent to those of amlodipine and Captopril. *I. cylindrica* has good antioxidant activity. Aqueous extract of *I. cylindrica* can increase the activity of superoxide dismutase (SOD) in the liver and brain tissue of mice with alcoholism, inhibiting the activity of hydroxyl radicals, lowering the level of malondialdehyde, enhancing the body's antioxidant status, and alleviating the pathological effects of oxidative stress to liver and brain tissue (Ruslin et al., 2013).

Bioactive components in *Centella asiatica* include asiatic acid, asiaticoside, madecassoside, terpenoids, and flavonoids. These compounds have pharmacological functions, including antihypertensive, antioxidant, anti-fibrotic, and cardio-renal protective effects. Against renovascular hypertensive rats, asiatic acid has a beneficial effect on the Ang II-AT1R-NADPH oxidase-NF-B pathway. Asiatic acid affects hemodynamic changes, the renin-angiotensin system (RAS), oxidative stress, and inflammation in hypertensive rats (Maneesai et al., 2017). *C. asiatica* exhibited good antioxidant and antihyperlipidemic properties and the highest phytochemical content. The presence of strong phenolic antioxidant components in *C. asiatica*, primarily gulonic acid, ferulic acid, kaempferol, chlorogenic acid, and asiatic acid, can confer significant antihyperlipidemic activity in HCF-induced rats (Kumari et al., 2016).

Syzygium polyanthum leaves have been traditionally used to treat diseases such as hypertension, diabetes, ulcers, diarrhea, and infectious skin diseases. This extract of plant leaves contains phenolic compounds, including caffeic acid, gallic acid, and 4-allyl-1,2-dihydroxybenzene (hydroxychavicol). *S. polyanthum*'s potential to reduce blood pressure. Intravenous administration of water and ethanol extract of *S. polyanthum* leaves at a typical dose of 20-100 mg/kg BW can significantly reduce high blood pressure in normal Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) (Ismail et al., 2013). According to Ismail et al.'s in vitro studies, the aqueous extract of *S. polyanthum* leaves (ASP) exhibits

dose-dependent ACE-inhibitory activity, acting in part via protein precipitation (Ismail et al., 2022). The antioxidant properties of *S. polyanthum* leaves were demonstrated by M.D. Hidayati. The methanol and ethyl acetate extracts of *S. polyanthum* leaves were shown to have antioxidant activity, with IC_{50} values of 17.46-24.09 g/mL and 13.70 g/mL, respectively (M. D. Hidayati et al., 2017).

3.5. Proposed mechanism of antihypertensive and antioxidant action

The jamu used in this study was identified as an antihypertensive. Our previous in vitro study found that this jamu exhibits antioxidant activity (IC_{50} = 11.4 ppm) and antihypertensive effects. Several mechanisms by which bioactive herbal plant compounds that activate antioxidant enzymes can reduce oxidative stress. Exogenous antioxidants derived from various flavonoid compounds and plant polyphenols have been shown in studies to improve kidney function by reducing oxidative damage and increasing the activity of antioxidant enzymes such as SOD and glutathione (Giribabu et al., 2014; Rojas-Rivera et al., 2012). The observed reduction in MDA levels, together with increased GSH and SOD levels, indicates an amelioration of renal oxidative stress. However, these findings should not be interpreted as direct evidence of renal protection, as renal function and histopathological changes were not assessed in the present study

This dual-action profile of the jamu formulations aligns with previous findings on flavonoid-rich herbal matrices, highlighting how secondary metabolites contribute to robust radical-scavenging activities. The antihypertensive effect observed in the present study may potentially involve mechanisms such as ACE inhibition or modulation of the RAAS, as suggested by previous studies. However, these mechanisms were not directly evaluated in the present study and therefore cannot be confirmed based on our findings (Verma et al., 2021). Nevertheless, certain parameters—including serum ACE activity, upstream renin and angiotensin II levels, renal histology, and specific kidney markers like serum creatinine and blood urea nitrogen—were not evaluated in the present work. Therefore, future investigations incorporating specific molecular and histopathological assays are warranted.

3.6. Study limitations

This study has several limitations. The relatively small sample size may limit the generalizability of the findings. Renal function and histopathological changes were not evaluated; therefore, the observed changes in MDA, GSH, and SOD should be interpreted as indicators of renal oxidative stress rather than direct evidence of renal protection. In addition, ACE activity, renin, and angiotensin II were not measured; thus, the mechanisms underlying the antihypertensive effects remain to be elucidated. Finally, as this study was conducted in a fructose-fed rat model, the findings cannot be directly extrapolated to humans. Further studies are needed to investigate the underlying mechanisms, safety, and clinical relevance of this formulation.

4. CONCLUSION

Administration of the standardized antihypertensive jamu formulation for 2 weeks at doses of 0.01, 0.02, and 0.03 g/kg BW twice daily attenuated blood pressure elevation in 10% fructose-induced rats and was accompanied by increased SOD activity and GSH levels and decreased MDA levels. These findings suggest that the jamu formulation has antihypertensive activity and may ameliorate renal oxidative stress under the experimental conditions. However, further studies are needed to determine the underlying mechanisms and to evaluate renal function, histopathological changes, and the potential clinical relevance of these effects.

AUTHOR CONTRIBUTIONS

Conceptualization, S.T.R. and A.R.Y.E.; methodology, S.T.R., A.R.Y.E., and A.Y.; formal analysis, S.T.R. and A.R.Y.E.; investigation, S.T.R., A.R.Y.E., Y.E., and A.Y.; data curation, Y.E. and A.Y.; writing—original draft preparation, S.T.R. and A.R.Y.E.; writing—review and editing, A.R.Y.E. and A.Y. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Health Research Ethics Committee (Institutional Review Board) of Universitas Esa Unggul (protocol number 0161-20.152/DPKEKEP/FINAL-ENUEUN/2020, approved on 30 May 2020).

INFORMED CONSENT STATEMENT

Not applicable, as this study did not involve human participants.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this work, the authors utilized Gemini AI-assisted technologies and language models solely to improve the grammatical precision, readability, and structural flow of the academic English narrative

within the Results and Discussion section. After using this tool, the authors thoroughly reviewed, edited, and verified all content to ensure scientific accuracy. The authors maintain full accountability for the intellectual integrity, authenticity of the data, factual correctness, and originality of the academic framework of the finalized manuscript.

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