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ORIGINAL ARTICLE

Nephroprotective and Hepatoprotective Effects of Ethanol Extract of *Eleutherine Bulbosa* (Mill) Urb in Hypertensive and Hyperlipidaemic Rats

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Abstract

Background/Aim: Hypertension and hyperlipidaemia are interrelated conditions that elevate the risk of cardiovascular diseases and contribute to the dysfunction of critical organs such as the liver and kidneys. *Eleutherine bulbosa* (Mill) Urb, known as Dayak onion, contains bioactive compounds like flavonoids, phenolics, quercetin derivatives and oxyresveratrol, which are believed to have nephroprotective and hepatoprotective effects due to their antioxidant and anti-inflammatory properties. This study aimed to evaluate the protective effects of the ethanol extract of Dayak onion on kidney and liver function in hypertensive and hyperlipidaemic rats.

Methods: The experimental design employed a pre-post-test control group over 28 days. Thirty-five male Wistar rats were divided into seven groups: Normal group, Negative control (given NaCl solution at a dose of 3.75 g/kg body weight and fed a high-fat diet), Positive control (captopril and simvastatin) and three Treatment groups (given Dayak onion ethanol extract (EEEB) suspension at doses of 100, 200 and 400 mg/kg body weight, respectively). Serum was extracted via the ophthalmic vein on days 22 and 29.

Results: Compared to the negative control group, this study showed that administering doses of 100, 200 and 400 mg/kg BW of EEEB was able to significantly lower blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT) and aspartate aminotransferase (AST) levels ($p < 0.05$). The dose of 400 mg/kg BW demonstrated the highest potential to protect the kidneys and liver, coming close to or matching the effects seen in the positive control group. In addition, the protective effect of EEEB on the kidneys and liver was compared to the positive control group (captopril and simvastatin).

Conclusion: Based on these findings, it can be concluded that EEEB protects against kidney and liver damage caused by hypertension and hyperlipidaemia.

Key words: Dayak onion; Blood urea nitrogen; Creatinine; Alanine transaminases; Aspartate aminotransferases; Hypertension; Hyperlipidaemias.

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Introduction

Hypertension and hyperlipidaemia are two interrelated pathologies and are major risk factors for cardiovascular disease.[1] Based on WHO data, the number of hypertension sufferers in the world in

2015-2020 reached 1.13 billion and is estimated to increase to 1.5 billion in 2025, with the highest prevalence in Southeast Asia.[2] In Indonesia, the prevalence rate of hypertension reaches 34.1 %, where these sufferers have a 3.2 times higher risk of experiencing kidney failure According to research, people with hyperlipidaemia are 3.5 times more likely to experience liver dysfunction, which can lead to diseases such as hepatitis and cirrhosis of the liver.[3]

Both conditions can potentially harm target organs, particularly the liver and kidneys, which are crucial in regulating blood pressure and cholesterol metabolism.[4] Too much salt (NaCl) can raise blood pressure, leading to high blood pressure. This can cause organ damage through several mechanisms. This includes increased oxidative stress and activation.[5, 6] The renin-angiotensin-aldosterone system (RAAS) constricts arterioles and increases intraglomerular pressure. As a result, the glomerulus is damaged and the glomerular filtration rate is reduced, which results in impaired kidney function.[7, 8] This is indicated by increased blood urea nitrogen (BUN) and creatinine levels. Hyperlipidaemia often occurs due to the consumption of high-fat foods, which contributes to the formation of atherosclerotic plaques due to increased oxidative stress and lipid accumulation in liver tissue.[9, 10] As a result, liver function is disrupted, characterised by increased levels of liver enzymes, namely serum glutamic pyruvic transaminase (SGPT/ALT) and serum glutamic oxaloacetic transaminase (SGOT/AST). If this condition is not treated, it can progress to liver fibrosis and cirrhosis.[11, 12]

Conventional treatments for hypertension and hyperlipidaemia, such as ACE inhibitors, calcium channel blockers, statins and fibrates, often cause dangerous side effects.[13, 14] Therefore, a therapeutic intervention is required that is effective in reducing both blood pressure and lipid levels while concurrently exerting a protective effect on the kidneys and liver.[15] This encourages the search for other safer and more affordable alternative treatments, one of which is by utilising natural ingredients. Dayak onion is an endemic plant of Kalimantan, which is of concern because it is traditionally used by the Dayak people for various treatments, including hypertension and metabolic disorders such as hyperlipidaemia, antioxidants, as well as nephroprotective and hepatoprotective agents.[16] This plant contains various groups of compounds, such as alkaloids, glycosides, flavonoids, phenolics, eleutherin, isoeleutherine, eleutherol and eleutherinol. By repairing liver and kidney cells, oxyresveratrol and flavonoid compounds with quercetin derivatives have anti-inflammatory and antioxidant properties that inhibit lipid peroxidation and neutralise free radicals (ROS), thereby reducing oxidative stress and restoring normal levels of BUN, creatinine, ALT and AST.[17]

The ethanol extract of Dayak onion has been shown to act as a nephroprotective agent by inhibiting the angiotensin-converting enzyme (ACE), which contributes to elevated blood pressure and reduced oxidative stress and inflammation in the kidneys.[16] Consequently, this effect can potentially reduce the levels of creatinine and BUN, which serve as the primary biomarkers of renal health. In addition, this plant also increases the production of nitric oxide (NO), which helps dilate blood vessels and maintain kidney function. From a hepatoprotective perspective, Dayak onions work by reducing fat accumulation in the liver through increased lipid metabolism and decreased LDL and triglyceride levels.[18] Flavonoids in this plant also have antioxidant effects that can reduce ALT and AST levels by increasing enzyme activity such as superoxide dismutase (SOD) and catalase, which play a role in neutralising free radicals that cause liver cell damage. In addition, Dayak onion extract is known to protect hepatocytes from inflammation and fibrosis by modulating the expression of pro-inflammatory cytokines.[19]

Several previous studies have examined the benefits of Dayak onions in lowering blood pressure and lipid levels, as well as their protective effects on the kidneys and liver. Examined the antihypertensive effect of ethanol extract of Dayak onion on fructose-induced hypertensive rats and found that blood pressure could be significantly reduced, followed by improvement in kidney function.[20] Dayak onion extract has been proven to be able to reduce LDL and total cholesterol levels and has a protective effect on the kidneys and liver. Meanwhile, literature review concluded that Dayak onion has the potential to be a nephroprotective and hepatoprotective agent due to its strong antioxidant and anti-inflammatory properties. Another study by also reported that Dayak onions have anti-inflammatory activity, which is useful in protecting the liver from the negative effects of hyperlipidaemia.[16]

However, although various studies have shown the benefits of Dayak onion in lowering blood pressure and cholesterol, studies that specifically examine its nephroprotective and hepatoprotective effects by measuring BUN, creatinine, ALT and AST levels are still minimal.[16] Therefore, this study aimed to evaluate the effects of Dayak onion ethanol extract (EEEB) in protecting kidney and liver function in rats with hypertension and hyperlipidaemia. BUN and creatinine levels were measured as indicators of kidney health, while ALT and AST levels were analysed to evaluate liver function. In addition, this study also aimed to understand the mechanism of action of Dayak onion extract in reducing oxidative stress and inflammation through the regulation of antioxidant and anti-inflammatory signalling pathways.

Methods

This research is an experimental laboratory study using a pre-posttest control group design. The tools used were analytical scales (AND GF-300, glassware (Pyrex®), water bath (Memmert), probe (Obsidi Medica®), oral syringe (Terumo®), capillary tube (Merck®), Eppendorf, EDTA tube (Reiged®), micropipette, yellow tip, blue tip, centrifuge and spectrophotometer (SHIMADZU). The materials used in this study were Dayak onions obtained from the city of Sintang, West Kalimantan and were determined at the UPT. Materia Medica Laboratory Batu, East Java with the number 000.9.3 / 2463 / 102.20 / 2024, in addition ethanol 96 % (CV. General Labora), NaCl 2 % (CV. General Labora), captropil dose 25 mg ®, simvastatin dose 10 mg ®, CMC-Na (CV. General Labora), Urea FS reagent, creatinine FS, ALT and AST (*Diasys*).

Animal

The test animals used in this study were male white rats of the Wistar strain (Rattus norvegicus) aged 2-3 months with a body weight of 200-250 g. As many as 35 rats were in healthy condition and showed normal activity. The rats were divided into seven groups consisting of five animals each: normal group (given CMC-Na 0.5 %), negative control (given NaCl dose of 3.75 g/kg BW and high fat diet feed), positive control (captopril and simvastatin) and 3 treatment groups (given EEEB doses of 100, 200 and 400 mg/kg BW). All treatments were given orally. Rats were maintained in a controlled environment with a temperature of 22 ± 2 °C and a relative humidity of 55 ± 10 %, a 12-hour light/dark cycle and unlimited access to food and water.

Making Dayak onion ethanol extract of *Eleutherine bulbosa* (EEEB)

The maceration process was carried out on 500 grams of dry Dayak onion simplex using 96 % ethanol solvent, with a ratio of 1:5 (500 grams of dry Dayak onion simplex with 2500 mL of ethanol) for 3 days. Furthermore, the separation between macerate and dregs from Dayak onion was carried out by filtering using filter paper. Then the dregs of Dayak onion were re-macerated using 96 % solvent as much as 1500 mL. The results of maceration and re-maceration were combined and evaporated using a rotary evaporator at 60 °C to produce a thick Dayak onion ethanol extract.

Preparation of induction solution and test solution

The induction solution given to the test animals consisted of NaCl at a concentration of 3.75 g/kg BW, which increased blood pressure. Made by dissolving in 100 mL of CMC-Na 0.5 %. While for increasing hyperlipidaemia levels, made by 20 % used cooking oil, 10 % beef fat and 20 % quail egg yolk, in CMC-Na 0.5 %, given orally 2 times a day. The EEEB test solution was made based on 3 dose variations, namely 100, 200 and 400 mg/kg BW, dissolved in 100 mL of 0.5 % CMC-Na solution.

Nephroprotective and hepatoprotective activity test

The test began with the acclimatisation of rats for 7 days and their conditions (physical, body weight and behaviour) were monitored during the acclimatisation period. Then, each normal group (0.5 CMC-Na solution), negative control group (3.75 g/kg body weight NaCl solution and high-fat diet), positive control group (captopril and simvastatin) and 3 treatment groups (each group of EEEB suspension 100, 200 and 400 mg/kg BW), given orally, for 21 days. Rats were said to be hypertensive if blood pressure is > 140/90 mm Hg and hyperlipidaemic if triglyceride levels were > 145 mg/dL. After both conditions improved, blood was taken on day 21 post-induction. Then continued with EEEB administration on days 22-28. Measurement of BUN and creatinine levels was on day 29.

Nephroprotective parameter testing (BUN and creatinine)

The test animals were fasted for ± 4 hours before being treated. Furthermore, blood was taken through the ophthalmic vein, using a capillary tube, then the blood was collected in an EDTA tube of ± 2 cc. Furthermore, the blood was centrifuged at 2500 rpm for 15 minutes. The serum obtained through centrifugation was then transferred to an Eppendorf tube to test creatinine and BUN levels. BUN level was examined using 10.0 µL of serum plus 1000.0 µL of reagent mix and in a vortex mixer until homogeneous and incubate for 1 minute at 20-25 °C. Absorbance was directly measured with a spectrophotometer after 30 seconds at a wavelength of 340 nm. Creatinine level examination was carried out using a sample of 50.0 µL plus 1000.0 µL of reagent mix and vortexed mixer until homogeneous, then incubated for 1 minute at a temperature of 20-25 °C. Absorbance was directly measured with a spectrophotometer after 60 seconds with a wavelength of 492 nm.

Hepatoprotective parameter testing (ALT and AST)

The assessment of ALT and AST levels entailed the amalgamation of Reagent I and Reagent II in a proportion of 4:1. A total of 100 µL of serum was added with 1000 µL of reagent kit, then incubated for 1 minute at a temperature of 20-25 °C. Then, read with a spectrophotometer at a wavelength of 340 nm, measurements were carried out at minutes 1, 2 and 3, at a temperature of 37 °C. Measurement of ALT and AST activity was based on changes from NADH to NAD+ + which is equivalent to changes in pyruvate to lactate in ALT and oxaloacetate to malate in AST.

Data analysis

Analyses of BUN, creatinine, ALT and AST measurement data measured before and after treatment were analysed using the IBM SPSS Statistics 23.0 program. Starting with the Kolmogorov-Smirnov test as an introduction and the Levene Test, the results showed that the data were normally distributed and homogeneous, then the parametric ANOVA and post hoc Tukey tests were carried out.

Results

Measurement of BUN, creatinine, ALT and AST levels was performed before and after administration of the extract. Blood samples were taken on day 22 for pretest data and day 29 for posttest data. Mice were fasted for ± 12 hours before blood sampling to minimise the effect of food on blood components. Blood was taken through the ophthalmic vein to ensure the accuracy of blood chemistry analysis results. Based on the results of measuring BUN levels before and after administering the extract, the average difference data for each group were produced, as can be seen in Table 1.

BUN level measurement

The results of data analysis using the post-Tuckey test showed a significant difference between the negative control group and the group given EEEB at doses of 100, 200, 400 mg/kg BW and the captopril group as a comparison. This significant difference was seen in BUN levels, where the EEEB treatment group 100 mg/kg BW (29.6 ± 7.9), 200 mg/kg BW (34.6 ± 5.3) and 400 mg/kg BW (36.0 ± 6.3) mg/dL each showed a decrease in levels compared to the negative control group. The captopril group experienced a similar decrease to the EEEB group, with a difference in levels (27.2 ± 6.7 mg/dL).

Creatinine level measurement

The following presents the results of creatinine level measurements in male rats. Table 2 shows the difference in average creatinine levels between groups and shows a comparison of measurements before and after treatment. The table provides a clear picture of the changes in creatinine levels that occurred in each treatment group.

Based on Table 2, in the negative control group there was an increase in creatinine levels with a mean difference of (0.21 ± 0.08), while the group given EEEB at doses of 100, 200 and 400 mg/kg BW showed a significant decrease in creatinine levels with a mean difference of 1.04 ± 0.23, 1.11 ± 0.23 and 1.18 ± 0.13 mg/dL compared to negative control. The captopril group also showed a decrease in creatinine levels with a mean difference value of (0.78 ± 0.20 mg/dL), indicating a positive effect of the treatment on kidney function.

Table 1: Average results of difference in blood urea nitrogen (BUN) levels before and after administration of Dayak onion ethanol extract (EEEB) on days 21-28

Group	Dose (mg/kg BW)	Mean ± SD BUN (mg/dL)		
		Before	After	Difference
Normal	-	18.2 ± 2.0 [a]	16.0 ± 1.0 [a]	2.2 ± 1.0 [a]
Negative control	-	69.6 ± 6.2 [c]	17.8 ± 2.6 [a]	51.8 ± 3.6 [c]
Captopril	4.5	44.2 ± 8.7 [b]	17.0 ± 1.6 [a]	27.2 ± 6.7 [b]
Simvastatin	0.9	41.6 ± 8.1 [b]	18.6 ± 1.3 [a]	23.0 ± 10.0 [b]
EEEB	100	46.6 ± 8.9 [b]	17.0 ± 1.0 [a]	29.6 ± 7.9 [b]
EEEB	200	51.0 ± 6.9 [b]	16.4 ± 1.5 [a]	34.6 ± 5.3 [b]
EEEB	400	54.8 ± 7.6 [b]	18.8 ± 1.3 [a]	36.0 ± 6.3 [b]

$p \leq 0.05$; significantly different from the negative control group; Values are presented as mean ± SD (standard deviation) (n = 5). If the superscript letters (a, b and c) in a column are different, then the difference is significant at $p < 0.05$ based on Tukey's test.

Table 2: Average results of difference in creatinine levels before and after administration of Dayak onion ethanol extract (EEEB) on days 21-28

Group	Dose (mg/kg BW)	Mean ± SD creatinine (mg/dL)		
		Before	After	Difference
Normal	-	0.52 ± 0.09 [a]	0.48 ± 0.07 [a]	0.04 ± 0.01 [a]
Negative control	-	2.12 ± 0.32 [c]	0.42 ± 0.15 [a]	1.70 ± 0.17 [b]
Captopril	4.5	1.48 ± 0.32 [b]	0.70 ± 0.13 [b]	0.78 ± 0.20 [b]
Simvastatin	0.9	1.48 ± 0.11 [b]	0.59 ± 0.15 [b]	0.89 ± 0.04 [b]
EEEB	100	1.62 ± 0.29 [b]	0.58 ± 0.06 [b]	1.04 ± 0.23 [b]
EEEB	200	1.63 ± 0.28 [b]	0.52 ± 0.06 [a,b]	1.11 ± 0.23 [b]
EEEB	400	1.65 ± 0.17 [b,c]	0.47 ± 0.04 [a]	1.18 ± 0.13 [c]

$p \leq 0.05$; significantly different from the negative control group; Values are presented as mean ± SD (standard deviation) (n = 5). If the superscript letters (a, b and c) in a column are different, then the difference is significant at $p < 0.05$ based on Tukey's test.

ALT level measurement

The measurement results show a difference in the average ALT levels between groups. This table shows the changes in ALT levels between the control group and the treatment group, both before and after the administration of the extract. As seen in Table 3, the average difference illustrates the effect of treatment on ALT levels, which are an important indicator in assessing liver function.

The findings of the comparative analysis between the negative control group, the EEEB and the positive control group, simvastatin, revealed a substantial discrepancy in the decline of serum glutamic-pyruvic transaminase (ALT) levels. The negative control exhibited a decline of 14.98 ± 0.49 U/L, while the groups administered EEEB at 100, 200 and 400 mg/kg BW demonstrated a decrease, with the 400 mg/kg BW group exhibiting the most pronounced decrease, reaching 72.16 ± 0.44 U/L. The simvastatin group also demonstrated a decrease of 54.87 ± 1.35 U/L.

AST level measurement

The measurement results showed that the difference in the average AST levels between groups could be seen clearly. This table presents the changes in AST levels in the control group and the treatment group, before and after the administration of the extract. This average difference reflects the impact of treatment on AST levels, which is an important indicator in assessing liver function, as seen in Table 4.

The findings indicated that the utilisation of EEEB

Table 3: Average results of difference in alanine transaminase (ALT) levels before and after administration of Dayak onion ethanol extract (EEEB) on days 21-28

Group	Dose (mg/kg BW)	Mean ± SD ALT (U/L)		
		Before	After	Difference
Normal	-	26.23 ± 1.42 [a]	19.47 ± 0.90 [a]	6.76 ± 0.52 [a]
Negative control	-	56.51 ± 2.43 [b]	41.53 ± 2.92 [d]	14.98 ± 0.49 [b]
Captopril	4.5	54.11 ± 2.78 [b]	27.39 ± 0.90 [c]	26.72 ± 1.88 [c]
Simvastatin	0.9	82.04 ± 2.22 [d]	27.17 ± 0.87 [c]	54.87 ± 1.35 [f]
EEEB	100	62.52 ± 1.65 [c]	24.11 ± 0.93 [b]	38.41 ± 0.72 [d]
EEEB	200	64.97 ± 2.03 [c]	21.31 ± 0.49 [a]	43.67 ± 1.54 [e]
EEEB	400	93.56 ± 0.65 [e]	21.40 ± 0.21 [a]	72.16 ± 0.44 [g]

$p \leq 0.05$; significantly different from the negative control group; Values are presented as mean ± SD (standard deviation) (n = 5). If the superscript letters (a, b and c) in a column are different, then the difference is significant at $p < 0.05$ based on Tukey's test.

Table 4: Average results of difference in aspartate aminotransferase (AST) levels before and after administration of Dayak onion ethanol extract (EEEB) on days 21-28

Group	Dose (mg/kg BW)	Mean ± SD AST (U/L)		
		Before	After	Difference
Normal	-	58.29 ± 4.98 [b]	53.08 ± 3.37 [a]	5.21 ± 1.60 [a]
Negative control	-	113.67 ± 8.32 [a]	78.80 ± 10.52 [c]	34.87 ± 2.20 [b]
Captopril	4.5	124.26 ± 4.64 [c]	60.40 ± 9.07 [a.b]	63.86 ± 4.43 [c]
Simvastatin	0.9	127.90 ± 6.82 [c]	67.64 ± 5.60 [b.c]	60.26 ± 1.22 [c]
EEEB	100	123.84 ± 6.20 [c]	54.28 ± 7.85 [a.b]	69.56 ± 1.65 [c]
EEEB	200	119.80 ± 11.39 [c]	60.90 ± 8.16 [a.b]	58.90 ± 3.23 [c]
EEEB	400	126.71 ± 2.12 [c]	47.92 ± 1.95 [a]	78.79 ± 0.17 [c]

$p \leq 0.05$; significantly different from the negative control group; Values are presented as mean ± SD (standard deviation) (n = 5). If the superscript letters (a, b and c) in a column are different, then the difference is significant at $p < 0.05$ based on Tukey's test.

substantially impacted the reduction of AST levels compared to the negative control groups. In contrast, the negative control decreased 34.87 ± 2.2 U/L. The administration of EEEB extract at doses of 100, 200 and 400 mg/kg BW resulted in a decline in AST levels, with the highest observed decrease of 78.79 ± 0.17 U/L recorded in the 400 mg/kg BW group. A similar trend was observed in the simvastatin group, which significantly decreased to 60.26 ± 1.22 U/L.

Discussion

Increased BUN and creatinine levels after 21 days of induction with NaCl and high-fat diet indicate increased oxidative stress and inflammation in the kidneys.[21,22] Excessive intake of NaCl can trigger hypertension, which may lead to increased blood pressure and decreased kidney function. The kidneys normally regulate the sodium levels in the body and excrete excess sodium in the urine.[23] However, if sodium intake is too high, the kidneys cannot remove it all and sodium will accumulate in the blood. This increase in blood sodium levels causes high blood pressure, worsens hypertension and interferes with kidney function.[24] Meanwhile, high-fat food consumption can trigger hyperlipidaemia, which contributes to kidney damage through oxidative stress and inflammation mechanisms. Fat accumulation in kidney tissue can disrupt endothelial function and trigger fibrosis, increasing blood BUN and creatinine levels. Oxidative stress damages various organs, including the kidneys. One factor that can trigger oxidative stress is exposure to

free radicals from used cooking oil. In this study, the groups were divided to evaluate the effects of EEEB by comparing it to the normal, negative and positive groups.[25] The results showed that the treatment group with doses of 100, 200 and 400 mg/dL had a protective effect on the kidneys and liver, due to a decrease to normal limits, for BUN levels (15-21 mg/dL), creatinine (0.2-0.8 mg/dL), ALT (10-40 µL) and AST (45.7-80.8 µL). The results of the decrease showed the same effect as the positive control captopril, which protects kidney function and inhibits oxidative stress by inhibiting the angiotensin-converting enzyme (ACE), which plays a role in the conversion of angiotensin I to angiotensin II.[26, 27] Reducing angiotensin II levels helps lower blood pressure, increase blood flow to the kidneys and reduce oxidative stress and inflammation. Meanwhile, the positive control, simvastatin, works as an HMG CoA reductase inhibitor, which plays a role in the cholesterol synthesis process and inhibits superoxide production, so it is effective in preventing or reducing oxidative stress.[28, 29] This is in line with research by Mutiah et al[30] and Prasetya[31] which showed that ethanol extract of *E bulbosa* is rich in bioactive compounds such as oxyresveratrol, quercetin and eleutherin, which have strong antioxidant and anti-inflammatory activities.

The decrease in BUN, creatinine, ALT and AST levels in EEEB is due to the content of active compounds such as quercetin, oxyresveratrol, flavonoids and phenolic compounds, which have antioxidant and anti-inflammatory activities. Has a nephroprotective effect on the kidneys of hypertensive and hyperlipidaemic rats.[32] In addition, these compounds work with similar mechanisms in counteracting free radicals, suppressing oxidative stress and reducing inflammation, which are the main factors in kidney damage (33). With its antioxidant activity, quercetin and oxyresveratrol play a role in improving glomerular filtration function and reducing the accumulation of nitrogenous waste products in the blood, thereby helping to lower BUN and creatinine levels. Strengthened by research, this states that the compound oxyresveratrol can protect against nephrotoxicity in rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) by reducing oxidative stress markers, increasing glutathione and catalase levels and decreasing malondialdehyde, urea and creatinine levels, thereby improving histological changes. Therefore, the combination of active compounds in Dayak onion has the potential to provide optimal protection against kidney damage due to hypertension and hyperlipidaemia.[34]

This study's findings align with previous studies showing that flavonoids in plant extracts protect the kidneys through antioxidant and anti-inflammatory mechanisms. Several studies have also reported that phenolic compounds in Dayak onions can increase the activity of antioxidant enzymes, such as SOD and catalase, which play a role in reducing kidney inflammation due to oxidative stress. The following is the mechanism of EEEB as a nephroprotective and hepatoprotective, as shown in the Figure 1.[16, 36]

Concurrently, the assessment of SGPT/ALT and SGOT/AST levels following the administration of EEEB revealed a substantial decline in levels across the three doses. This observation indicates that EEEB exerts a hepatoprotective effect.[16] Therefore, it can be postulated that Dayak onion extract may safeguard hepatic cells from injury in hypertension and hyperlipidaemia. This protective mechanism can be attributed to the bioactive content present in Dayak onions, particularly flavonoids and phenolics such as quercetin and oxyresveratrol, which possess antioxidant and anti-inflammatory properties.[37] Specifically, quercetin has been demonstrated to play a pivotal role in the inhibition of free radical production and the augmentation of antioxidant enzyme activity, such as SOD and catalase. Collectively, these enzymes contribute to the alleviation of oxidative stress and inflammation in target tissues. Meanwhile, oxyresveratrol, as part of the stilbenoid group with flavonoids and other phenolic compounds, neutralises free radicals through electron or hydrogen transfer mechanisms, thereby inhibiting lipid peroxidation and preventing damage.[38]

Oxyresveratrol compounds have demonstrated the capacity to counteract the effects of free radicals, thereby diminishing the primary catalyst for oxidative stress within the hepatocellular system. Consequently, these compounds have been shown to safeguard hepatic cells from potential harm caused by metabolism and exposure to toxins.[39] In addition, this compound has been shown to inhibit pro-inflammatory enzymes and inflammatory mediators, thereby reducing inflammation and preventing further damage to liver tissue. Research conducted by and demonstrated that oxyresveratrol can reduce liver enzyme levels and improve liver tissue conditions in cases of damage caused by paracetamol and ethanol. The capacity to diminish oxidative stress and inflammation signifies that this phenomenon is instru-

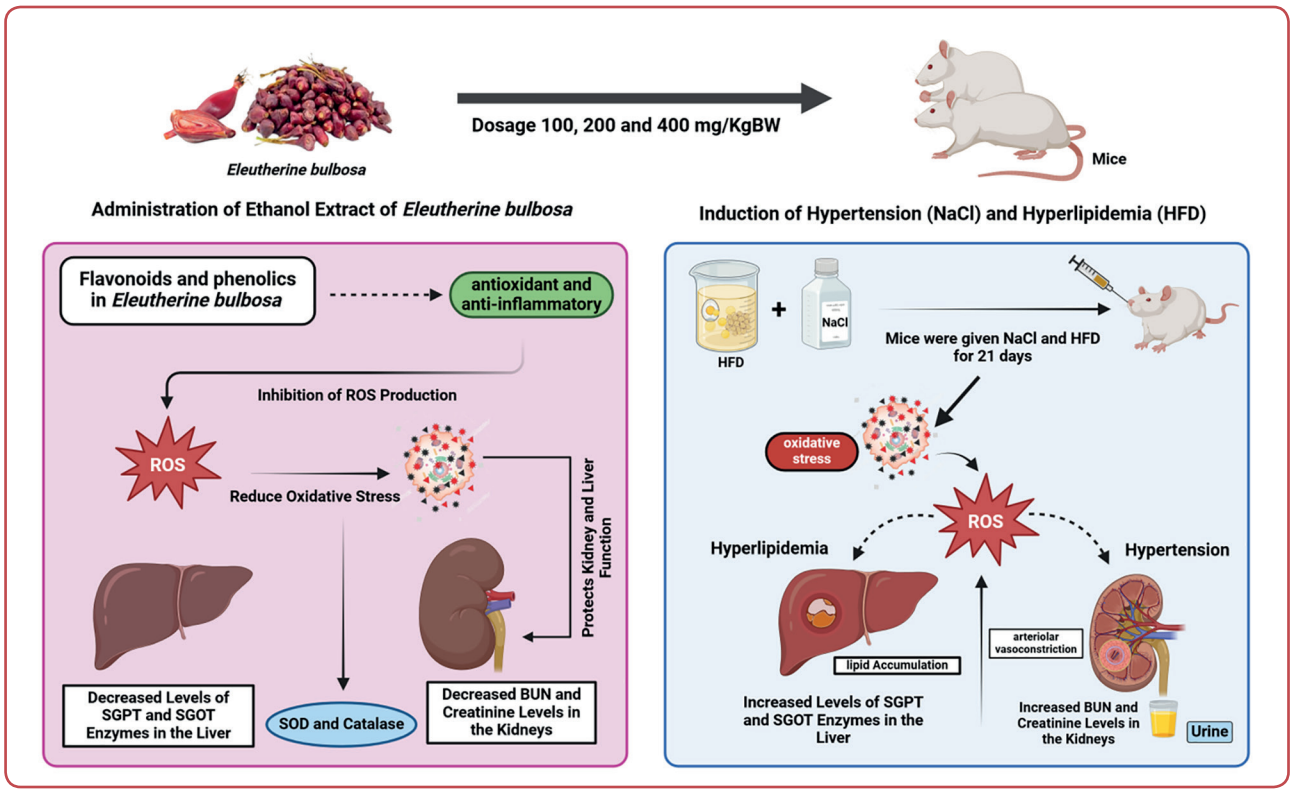

Figure 1: Induction mechanism of NaCl + high-fat diet (HFD) and Dayak onion ethanol extract (EEEB) administration

mental in preserving hepatocyte membrane stability, curtailing liver cell necrosis and enhancing compromised liver function.[39]

This study's results align with previous studies, which revealed that flavonoid compounds in plant extracts have hepatoprotective effects by inhibiting oxidative stress and inflammation. Other research conducted stated that flavonoids in this plant also have antioxidant effects that can reduce ALT and AST levels by increasing the activity of enzymes such as SOD and catalase, which play a role in neutralising free radicals that cause liver cell damage. In addition, the content of phenolic compounds in Dayak onions is also known to play a role in accelerating hepatocyte regeneration and reducing fat accumulation in the liver, which often occurs in hyperlipidaemia and can worsen hepatotoxicity. Therefore, Dayak onion extract has the potential as a nephroprotective and hepatoprotective agent, which can be further developed as a complementary therapy in treating kidney and liver dysfunction due to hypertension and hyperlipidaemia.

Conclusion

The ethanol extract of Dayak onion has been found to contain flavonoids, phenolics and oxyresveratrol, which have been identified as potential nephroprotectors and hepatoprotectors. The study demonstrated a significant ($p < 0.05$) reduction in BUN, creatinine, ALT and AST levels at 100, 200 and 400 mg/kg BW compared to the negative control group. The protective effect of EEEB on the kidneys and liver was compared to positive controls (captopril and simvastatin), where a dose of 400 mg/kg BW yielded the best results, nearly equivalent to the positive control. In light of these findings, it can be concluded that the ethanol extract of Dayak onion possesses the potential to serve as an effective protective agent against damage to the kidneys and liver caused by hypertension and hyperlipidaemia. However, it is imperative to emphasise the necessity for further research, in the form of clinical trials on humans, to ascertain the safety and efficacy of this extract at higher doses.

Ethics

This study (The study entitled "The Effect of Ethanolic Extract of Dayak Onion (*Eleutherine bulbosa* (Mill.) Urb) on Hypertension, Hyperlipidemia, and Kidney and Liver Function in Rats Induced by NaCl and High-Fat Diet") was reviewed and approved by the Research Ethics Committee of Universitas Ahmad Dahlan, Yogyakarta, Indonesia, decision number 012411355, dated 12 December 2024. All procedures involving animals were conducted in accordance with ethical guidelines for the use of laboratory animals and approved protocols.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Software: MM
Validation: DPA
Formal analysis: MSB, LHN, DE, DPA, MM
Investigation: MSB
Data curation: MSB
Writing - original draft: SK
Writing - review and editing: MSB, LHN, DE, MM
Supervision: SK, DPA.

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