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Original Research Article

The Effect of Ethanol Extract from *Salacca zalacca* (Gaertn.) Voss Peel on Antioxidant and Uric Acid Levels in Hyperuricemia Rats

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ABSTRACT

Hyperuricemia is a metabolic condition defined by excessive uric acid levels in the bloodstream. This condition may cause oxidative stress and reactive oxygen species (ROS) generation, overwhelming cellular antioxidant defense systems. Ethanol extract from snake fruit (*Salacca zalacca* peel (SZP)) contains bioactive compounds with potential antihyperuricemic properties, making it a promising alternative to conventional treatments like allopurinol. The mechanism of action is associated with the level of uric acid, superoxide dismutase (SOD), and malondialdehyde (MDA). Therefore, this research aimed to evaluate the impact of SZP on the level of SOD, MDA, and uric acid in male Wistar rats induced by chicken liver (CL) juice. A total of 30 rats were assigned to five groups, namely group I (control); II (hyperuricemia without any intervention), III (hyperuricemia treated with 1.8 mg/200 g BW allopurinol), IV, and V (hyperuricemia that were administered SZP at doses of 210 mg/kg BW and 420 mg/kg BW, respectively). The results showed significant reductions in uric acid levels (5.78 ± 0.10 mg/dL) and MDA (3.34 ± 0.28 nmol/mL) with the higher doses of SZP treatment (420 mg/kg BW). However, SOD levels increased (73.77 ± 2.00%) compared to the hyperuricemia control. The average SOD and MDA levels exhibited notable variations across all groups ($p < 0.05$). These findings suggested that ethanol extract from SZP effectively modulates oxidative stress and uric acid metabolism by influencing the serum levels of SOD, MDA, and uric acid and could serve as an alternative treatment for hyperuricemia.

Keywords: Antioxidant, Chicken liver, Malondialdehyde, *Salacca zalacca* peel, Superoxide dismutase, Uric acid.

Introduction

Hyperuricemia is a chronic metabolic disorder ranking fourth globally in prevalence, following hyperglycemia, hyperlipidemia, and hypertension.[1] This condition is caused by elevated blood uric acid due to impaired purine metabolism, which can occur both inside (genetically endogenous factors) and outside the body (exogenous factors from dietary purines).[2,3] Foods rich in purines, including seafood, red meat, poultry, offal (liver and kidney), nuts, certain fruits, and mushrooms worsen the condition.[4,5]

Excess uric acid contributes to oxidative stress by producing reactive oxygen species (ROS) in the blood vessel endothelium, disrupting the balance between ROS production and antioxidant defense.[6] Malondialdehyde (MDA), a byproduct of lipid peroxidation, serves as an oxidative stress biomarker,[7] while superoxide dismutase (SOD), an endogenous antioxidant, is diminished under these conditions. The binding of xanthine and xanthine oxidase (XO), with the inflammatory response further contributes to ROS production.[8]

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Snake fruit *Salacca zalacca* (Gaertn.) Voss contains flavonoid compounds classified as exogenous antioxidants.[8] Furthermore, Pondoh variety, cultivated in Indonesia, has particularly high flavonoid content in its peel among other varieties.[9] This study used ethanol extraction to isolate bioactive compounds to preserve flavonoids for antioxidant properties effectively.[8] Flavonoids from *Dissotis rotundifolia* have been shown to enhance levels of SOD and glutathione (GSH) in rats with gastric mucosal damage.[10] Kerehau leaf (*Callicarpa longifolia* Lamk.) flavonoids can reduce serum MDA levels induced by alloxan.[11] A previous study showed that flavonoids of *Cyclocarya paliurus* leaf inhibit lipid peroxidation and increase SOD activity.[12] *S. zalacca* inhibits the formation of ROS by donating H^+ atoms, thereby stabilizing radical compounds and stopping lipid peroxidation reactions.[13]

Several studies have shown that administering ethanol extract from *S. zalacca* reduces uric acid and increases antioxidant levels. Despite this benefit, the effect of ethanol extract from *S. zalacca* on SOD and MDA levels remains unclear. Therefore, this study aimed to investigate the effect of ethanol extract from *S. zalacca* peel (SZP) on antioxidant and uric acid levels of hyperuricemia rats induced by chicken liver (CL). CL comprises a high purine (ranging from 100 to 1000 mg per 100 g of dietary components),[14] mimicking dietary-induced hyperuricemia in humans.

Materials and Methods

Plant material and extraction

Samples of SZP were obtained from collectors in Nglumut, Magelang, Indonesia (7° 36' 50" S, 110° 21' 27" E) in July 2023. A voucher specimen, labeled FKSA-SZP5-VI22, was deposited in the Biomedical Laboratory at Universitas Islam Sultan Agung, Semarang, Indonesia.

The collected samples were sorted, cut, and subsequently dried using a drying cabinet at 40°C until the water content was <10%. Dried SZP was blended to produce a fine powder. The extract was produced by macerating the sample in a 1:10 ratio of ethanol (96%, analytical grade, Merck, Germany) for 4 days with occasional stirring.[15] Filtration and evaporation processes were carried out to remove ethanol content in the extract. Distilled water was added to form a thick ethanol extract. Ethanol extract from SZP was administered at 210 mg/kg and 420 mg/kg daily.

Experimental design

A total of 30 male Wistar rats (3 months old, 190 - 210 g) were randomly assigned to five groups. Each group comprised six rats housed in a cage (25°C, 12:12-hour light/dark cycle) at the Center for Food and Nutrition Studies at Gadjah Mada University in Yogyakarta. The handling of animals in this study was conducted in compliance with international regulations concerning laboratory animal welfare. Rats were acclimated for 7 days and given standard pellets and distilled water *ad libitum* before the experiment, followed by the induction of hyperuricemia using CL for 10 days. CL juice 8 g was used due to the high purine levels and availability in Indonesia. Group I served as the normal control while II was induced with CL. Group III was induced with CL and given allopurinol (1.8 g/200 g BW) for the next 7 days. IV and V were induced with CL and given SZP at doses 210 and 420 mg/kg BW, respectively, for the subsequent 7 days. This study was approved by the Medical Research Bioethics Commission, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia (524/XII/2022/Bioethics Commission).

The measurement of uric acid levels

The determination of uric acid levels was conducted after the induction of CL for 10 days before allopurinol and SZP (pre-test) and after treatment for 7 days (post-test). Blood was collected by inserting a hematocrit pipette into the orbital sinus at a 45-degree angle and transferred to a tube.[16] After centrifugation (3500 rpm) for 15 min, serum was obtained. UV-Vis spectrophotometer (Thermo Fisher Scientific, USA) was used to measure serum uric acid using the Uricase method with Lipid Clearing Factor (LCF).[17,18]

The determination of SOD and MDA levels

SOD and MDA levels were determined after allopurinol and SZP treatment. Blood without an anticoagulant was set aside for 15 min in a tube. The serum was centrifuged for 15 min at 4500 rpm and SOD levels were measured using ELISA Kit Reader (Thermo Fisher Scientific, USA) at 450 nm. Thiobarbituric Acid Reactive Substances (TBARS) assay was utilized to determine MDA levels using UV-Vis spectrophotometer at 532 nm. The 0.5 mL serum was added with 1.25 cc of Trichloroacetic acid (TCA, 40%, Sigma-Aldrich, USA), hydrochloric acid (HCl, 1N, Merck, Germany) 2.5 µL each, 200 µL 1 N HCl, 0.5 mL distilled water (Millipore, USA), and 100 µl sodium thiosulfate (NaThio, Sigma-Aldrich, USA). Subsequently, the substance was homogenized, heated at 1000°C for 25 min, and centrifuged (Thermo Scientific, USA) at 3000 rpm for 5 min to collect the supernatant. MDA levels were analyzed using a UV-Vis spectrophotometer (Thermo Fisher Scientific, USA) at 532 nm.[19,20]

Statistical analysis

Data analysis was conducted using SPSS version 25.0 for Windows (IBM Corp., Armonk, New York, USA). Non-parametric analysis of serum uric acid reduction was conducted using Kruskall-Wallis and Mann-Whitney tests, with p-values<0.05 indicating statistically significant. The Shapiro-Wilk and Levene tests were applied to assess data normality and homogeneity for uric acid, serum SOD, and MDA reduction, followed by a one-way Analysis of Variance (ANOVA) and post-hoc Least Significant Difference (LSD) test if applicable.

Results and Discussion

The results of analysis of mean serum uric acid levels pre- and post-intervention

Post-intervention analysis showed a substantial decrease in uric acid levels in groups receiving SZP at doses of 210 mg/kg BW and 420 mg/kg BW (Table 1). Doubling the dose of SZP led to a notable reduction in serum uric acid levels. Flavonoids from SZP (Tetramethoxyflavanone, Genistein, Hesperidin, and Kaempferol)[21] inhibit XO by competitively binding to its active site, reducing uric acid accumulation[22]. Their efficacy depends on hydroxyl or oxygen-containing groups, which enhance enzyme interaction. Only specific positions on flavonoid rings (C2, C3, C4, C5, and C7) contribute to this inhibitory effect.[23]

Table 1: Uric acid levels pretest and post-test, and the reduction in uric acid levels due to the administration of *Salacca zalacca* peel extract

Group	Mean Uric Acid Levels (mg/dL)		Δ Uric Acid Level (mg/dL) (pretest-posttest)
	Pretest	Post-test	
Group I	1.65±0.15	1.75±0.16	-0.10±0.02
Group II	8.07±0.24	8.37±0.24	-0.30±0.02
Group III	8.04±0.23	3.01±0.18	5.03±0.06
Group IV	8.03±0.18	3.03±0.14	5.00±0.05
Group V	8.01±0.14	2.22±0.06	5.78±0.10

Note: Results represent mean ± SD (n = 6).

Allopurinol was used as standard therapy for comparison. The liver metabolizes allopurinol, converting the substance into oxypurinol as the active metabolite. Both allopurinol and oxypurinol inhibit XO facilitating the suppression of hypoxanthine conversion into xanthine and subsequently into uric acid.[24] Table 2 shows the Mann-Whitney test between groups ($p = 0.004$, $p<0.05$), suggesting a significant difference. The reduction of serum uric acid levels between groups III and V was significantly different. This difference could be associated with the superior performance of flavonoid compounds in ethanol extract from SZP at 420 mg/kg BW compared to allopurinol at 1.8 mg/200 g BW.

Table 2: The Mann-Whitney test results on the reduction of serum uric acid levels in all groups

Uric acid levels	Group I	Group II	Group III	Group IV	Group V
Group I	-	0.004*	0.004*	0.004*	0.004*
Group II	0.004*	-	0.004*	0.004*	0.004*
Group III	0.004*	0.004*	-	0.418	0.004*
Group IV	0.004*	0.004*	0.418	-	0.004*
Group V	0.004*	0.004*	0.004*	0.004*	-

Note: *There is a significant difference between the groups ($p<0.05$)

The results of analysis of mean serum SOD levels post-intervention
SOD is an antioxidant enzyme that metabolizes oxygen radicals at a high reaction rate through an oxidation or reduction cycle.[25] SZP has a potent antioxidant capacity in the range of 50–100 ppm,[8] and the mean serum SOD levels are shown in Table 3. Group II exhibited a significant decrease (31.14 ± 2.32%), suggesting a high reactive oxidative stress. Increased levels of free radicals in the body cause a decrease in enzymatic antioxidants and inhibition of nuclear factor erythroid 2-related factor 2 (Nrf2).[8] Groups III, IV, and V significantly increased due to the intervention of allopurinol and SZP effectively improving oxidative stress conditions and high levels of enzymatic-type endogenous antioxidants. Furthermore, polyphenolic compounds, such as flavonoids, are found in phytochemical tests of SZP. These compounds can activate SOD and Nrf2, which stimulate SOD production.[8] According to Khalaf, the administration of allopurinol could increase SOD levels in the body,[26] which aligns with the findings of this study, showing a notable increase in SOD levels in group III. Treatment with *S. zalacca* extracts significantly elevated the SOD levels in zebrafish embryos at a dose of 0.4 mg/mL.[21]

Table 3: The mean serum levels per group post-intervention (%)

Group	Mean	
	SOD levels ± SD (%)	MDA levels ± SD (%) (nmol/mL)
Group I	87.54 ± 1.76	0.91 ± 0.12
Group II	31.14 ± 2.32	10.91 ± 0.36
Group III	62.62 ± 2.03	4.10 ± 0.24
Group IV	57.38 ± 1.87	4.47 ± 0.19
Group V	73.77 ± 2.00	3.34 ± 0.28

Note: Results represent mean ± SD (n = 6)

SOD captures ROS produced in the uric acid metabolism process and is broken down by GSH into hydrogen peroxide, which then converts back into a non-toxic form. Furthermore, flavonoids induce GSH synthesis[27] and increase the production of antioxidants SOD and GSH peroxidase, thereby preventing ischemia. Total flavonoid content inhibits signaling pathways in nuclear factor kappa B (NF-κB) by promoting the activation of adenosine monophosphate protein kinase (AMPK) and inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[27] The One-Way ANOVA resulted in a p-value of 0.000 ($p < 0.05$), indicating a significant difference in SOD levels across five groups. To further investigate the relevance, an LSD post hoc analysis was done, as shown in Table 4.

Table 4: The post hoc LSD results of serum SOD levels between test groups

Serum SOD levels	Group I	Group II	Group III	Group IV	Group V
Group I	-	0.000*	0.000*	0.000*	0.000*
Group II	0.000*	-	0.000*	0.000*	0.000*
Group III	0.000*	0.000*	-	0.080	0.001*
Group IV	0.000*	0.000*	0.080	-	0.001*
Group V	0.000*	0.000*	0.000*	0.001*	-

Note: *There is a significant difference between the groups ($p<0.05$)

This result suggests that the administration of SZP as an antioxidant may potentially alleviate oxidative stress in individuals with hyperuricemia.

The results of the analysis of mean serum MDA levels post-intervention
The serum MDA level of group I (0.91 nmol/mL) was used as the reference. Induction CL increased serum MDA with Group II showing the highest level (10.91 nmol/mL) and Group I the lowest (0.91 nmol/mL). According to a previous study, increased free radical production elevates lipid peroxidation, causing more physical damage[28] and higher serum MDA levels. Lower MDA levels could show decreased ROS production, as direct examination is difficult to conduct.[29] Hyperuricemia contributes to oxidative stress through XO activity, inflammation, and the catalysis of lipid peroxidation through lipoxygenase activity.[8,28,30] Serum MDA levels in Groups IV and V decreased significantly to 4.47 nmol/mL and 3.34 nmol/mL, respectively, compared to II. The exogenous antioxidant from SZP contains flavonoids,[8] which become natural antioxidants through the reduction of free radicals in an electron-donor mechanism and inhibit lipid peroxidation by donating one H^+ atom to free radicals and reducing MDA formation.[13] Therefore, Group V (SZP 420 mg/kg BW) showed the most effective treatment in reducing serum MDA levels.
The serum MDA levels in Group III (4.10 ± 0.24 nmol/mL), which received allopurinol, exhibited a significant reduction compared to Group II ($p = 0.000$) (Table 5).

Table 5: The post hoc LSD results of serum MDA levels between test groups.

Serum MDA levels	Group I	Group II	Group III	Group IV	Group V
Group I	-	0.000*	0.000*	0.000*	0.000*
Group II	0.000*	-	0.000*	0.000*	0.000*
Group III	0.000*	0.000*	-	0.030*	0.000*
Group IV	0.000*	0.000*	0.030*	-	0.000*
Group V	0.000*	0.000*	0.000*	0.000*	-

Note: *There is a significant difference between the groups ($p<0.05$)

Administering allopurinol lowers uric acid by suppressing the activity of the XO enzyme in the metabolism of hypoxanthine into uric acid.[31] However, prolonged use of allopurinol may cause side effects including gastrointestinal disorders, allergies, peripheral neuritis, aplastic anemia, hepatitis, and kidney disease.[32] These results are different from the report of previous studies, where allopurinol significantly reduced MDA levels due to higher the dose used (2.52 mg/head/day) compared to 1.8 mg/200 g BW/day. The significant decrease in serum MDA levels in group II (p-value = 0.000) is consistent with a previous study[33] attributed to the antioxidant effect of *S. zalacca*. Phenolic compounds, such as flavonoids exhibit antioxidants, XO enzyme inhibitors, and anti-inflammatory effects, reducing the production of free radicals in hyperuricemia. These compounds also act as ROS terminators by donating an electron and producing unreactive intermediate compounds.[8] Flavonoids in SZP play a significant role in reducing MDA levels, thereby preventing the formation of inflammatory mediators, NADPH, and ROS.[34]
According to the results, SZP has antioxidant properties and is effective in lowering uric acid levels in hyperuricemia rats by increasing SOD and reducing MDA levels. However, this study is limited by the absence of standard feed restrictions, which could influence the level of oxidative stress.

Conclusion

In conclusion, this study showed that ethanol extract from SZP had anti-hyperuricemic effects and influenced the serum levels of SOD, MDA, and uric acid. Therefore, the extract could be used as a new therapy for hyperuricemia. Future studies will focus on clinical validation, a crucial step in translating results into practical applications that could inform and enhance patient care.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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