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Original Article

Salacca zalacca peel modulates uricemia and IL-6 in rats

[La cáscara de *Salacca zalacca* modula la uricemia y la IL-6 en ratas]

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Abstract

Context: Hyperuricemia promotes oxidative stress and inflammation. Ethanolic salak (*Salacca zalacca*) peel extract (ESP) contains flavonoids with antioxidant potential.

Aims: To evaluate the effects of ESP on serum uric acid (UA), interleukin-6 (IL-6), and glutathione peroxidase (GPx) protein levels in hyperuricemic rats.

Methods: Male Wistar rats (n=30) were allocated to five groups (normal control; hyperuricemic control; allopurinol 9 mg/kg; ESP 210 or 420 mg/kg). Hyperuricemia was induced using a high-purine chicken-liver regimen. UA was measured pre- and post-treatment by a uricase-peroxidase colorimetric assay (520 nm). IL-6 and GPx protein levels were determined by enzyme-linked immunosorbent assay (ELISA) (450 nm).

Results: ESP 420 mg/kg reduced UA to 2.22 ± 0.06 mg/dL (Δ5.78 ± 0.10), lowered IL-6 to 32.96 ± 1.51 pg/mL, and increased GPx protein levels to 51.19 ± 0.72 pg/mL. Group differences were significant (ANOVA, p<0.001), with a dose-response trend for ESP.

Conclusions: ESP modulated uric acid, IL-6, and GPx in hyperuricemic rats, supporting its potential as a natural adjuvant for the management of hyperuricemia.

Keywords: glutathione peroxidase; hyperuricemia, interleukin-6; *Salacca zalacca*; uric acid.

Resumen

Contexto: La hiperuricemia promueve el estrés oxidativo y la inflamación. El extracto etanólico de cáscara de salak (*Salacca zalacca*) (ESP) contiene flavonoides con potencial antioxidante.

Objetivos: Evaluar los efectos del ESP sobre los niveles séricos de ácido úrico (AU), interleucina-6 (IL-6) y glutatión peroxidasa (GPx) en ratas hiperuricémicas.

Métodos: Se asignaron ratas Wistar macho (n = 30) a cinco grupos (control normal; control hiperuricémico; alopurinol 9 mg/kg; ESP 210 o 420 mg/kg). La hiperuricemia se indujo mediante una dieta rica en purinas a base de hígado de pollo. El AU se midió antes y después del tratamiento mediante un ensayo colorimétrico de uricasa-peroxidasa (520 nm). Los niveles de IL-6 y GPx se determinaron mediante ensayo inmunoenzimático (ELISA) (450 nm).

Resultados: ESP 420 mg/kg redujo el ácido úrico a 2,22 ± 0,06 mg/dL (Δ5,78 ± 0,10), disminuyó la IL-6 a 32,96 ± 1,51 pg/mL e incrementó los niveles de proteína GPx a 51,19 ± 0,72 pg/mL. Las diferencias entre grupos fueron significativas (ANOVA, p<0,001), observándose una relación dosis-respuesta para ESP.

Conclusiones: ESP moduló el ácido úrico, la IL-6 y la GPx en ratas hiperuricémicas, lo que respalda su potencial como coadyuvante natural para el tratamiento de la hiperuricemia.

Palabras Clave: ácido úrico; glutatión peroxidasa; hiperuricemia; interleucina-6; *Salacca zalacca*.

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Abbreviations: $AlCl_3$: Aluminum chloride; ANCOVA: Analysis of covariance; ANOVA: Analysis of variance; BW: Body weight; CL: Chicken liver; ESP: Ethanol extract from *Salacca zalacca* peel; $FeCl_3$: Ferric chloride; GPx: Glutathione peroxidase; IL-6: Interleukin-6; NF-κB: Nuclear factor kappa-B; ROS: Reactive oxygen species; SD: Standard deviation; TFC: Total flavonoid content; UA: Uric acid; UV-Vis: Ultraviolet-visible spectrophotometer; XO: Xanthine oxidase.

INTRODUCTION

Hyperuricemia is characterized by elevated serum uric acid resulting from increased production or reduced renal excretion (Jin et al., 2012). Its prevalence has risen in Asia, including Indonesia, where comparable hyperuricemia rates have been reported, reaching 18.6% in Depok City, West Java, and 18.2% in Denpasar, Bali (Butler et al., 2021). Oxidative stress and inflammation, particularly IL-6 upregulation, are central to hyperuricemia-related pathology, while antioxidant defenses such as glutathione peroxidase (GPx) are impaired. The condition arises primarily due to excessive UA production or decreased excretion, influenced by genetic factors and environmental exposures (Merriman, 2015). Consumption of high-purine foods, such as chicken liver, can trigger this condition.

In biological systems, oxidative stress reflects an imbalance where the generation of reactive oxygen species (ROS) exceeds the capacity of antioxidant defenses (Gil-Del Valle et al., 2023). Hyperuricemia induces oxidative stress that promotes inflammation and alters antioxidant defenses (Zhou et al., 2018). Elevated interleukin-6 (IL-6) levels further stimulate ROS production and downregulate antioxidant defense mechanisms, such as GPx. GPx neutralizes ROS and protects cells from oxidative damage (Afzal et al., 2023).

The standard therapeutic approach for hyperuricemia often involves xanthine oxidase (XO) inhibitors, such as allopurinol. However, prolonged allopurinol use may cause various adverse effects, including gastrointestinal, allergic, and organ-related complications. Conversely, natural alternatives with antioxidant properties have demonstrated efficacy in reducing uric acid levels in hyperuricemia, primarily by increasing superoxide dismutase (SOD) activity and decreasing malondialdehyde (MDA) levels (Pertiwi et al., 2025). Consequently, there is growing interest in identifying natural alternatives with antioxidant and anti-inflammatory properties.

Salacca zalacca (Gaertn.) Voss (family *Arecaceae*), commonly known as salak, is a tropical palm widely cultivated in Indonesia, with Salak Pondoh being one of the commercialized varieties indigenous to Yogyakarta (Farianti Djaafar et al., 2024; Ilmiah et al., 2021). The fruit is traditionally consumed for its presumed health benefits, including ethnomedical uses for metabolic and cardiovascular health, as well as for its alkaloids, flavonoids, tannins, and saponins (Handayani et al., 2021). These properties provide safer options for treating hyperuricemia, which is defined as a state of oxidative stress and chronic low-grade inflammation rather than by elevated uric acid (Chang et al., 2020; Yan et al., 2023). Despite its ethnomedical relevance, *S. zalacca* remains mechanistically underexplored, particularly its non-edible peel, which is often discarded despite being a rich source of antioxidant and anti-inflammatory compounds (Belmonte-Herrera et al., 2022). Although the antioxidant potential of *S. zalacca* and its effects on selected oxidative stress markers have been reported (Čepková et al., 2021; Husnul et al., 2021; Ilmiah et al., 2021), comprehensive *in vivo* studies linking uric acid regulation to inflammatory and antioxidant biomarkers remain limited. Thus, studies that concurrently measure uric acid and key mediators of inflammation and antioxidant defense are needed to clarify the pharmacological relevance of *S. zalacca* peel extract in hyperuricemia (Ashraf et al., 2024; Chang et al., 2020; Yan et al., 2023).

What distinguishes this study from previous research is the use of an ethanol extract of *S. zalacca* peel (ESP) to assess not only uric acid levels but also its effects on key inflammatory (IL-6) and antioxidant (GPx) biomarkers involved in hyperuricemia-associated oxidative stress, thereby complementing earlier findings on uric acid, superoxide dismutase, and malondialdehyde (Pertiwi et al., 2025). Other previous studies involving ESP, such as the work by Priyatno et al. (2012), used different varieties and evaluated different biological endpoints. Our study presents original *in vivo* data on the modulation of IL-6 and GPx, providing new insights into how *S. zalacca* peel extract may mitigate inflammation and oxidative damage induced by hyperuricemia.

To date, the combined effects of *S. zalacca* var. pondoh peel extract on inflammatory (IL-6) and antioxidant (GPx) biomarkers have not been jointly evaluated in a diet-induced hyperuricemia model. This study, therefore, aims to evaluate the effects of ESP on serum uric acid, IL-6, and GPx protein levels in hyperuricemic rats. It was hypothesized that ESP administration would reduce serum UA and IL-6 and increase GPx protein levels in hyperuricemic rats in a dose-dependent manner.

MATERIAL AND METHODS

Plant material

Fruit peels of *Salacca zalacca* var. pondoh were collected in Nglumut, Magelang (7°36′50″S, 110°21′27″E) in July 2023, and a voucher specimen (FKSA-SZP5-

VI22) was identified and deposited at the Biomedical Laboratory, Universitas Islam Sultan Agung, Semarang, Indonesia.

Preparation of ethanol extract of *S. zalacca*

Plant materials were dried in an oven at 40°C to constant weight and ground to a fine powder. Powdered material (1:10, w/v) was macerated in 96% ethanol for 72 h with occasional stirring. The extract was filtered, and the filtrate was concentrated by rotary evaporation (IKA RV10). The concentrated extract was air-dried, weighed to determine extraction yield (g extract/g dry material), and stored at −20°C until use (batch codes: ESP-0723-A and ESP-0723-B). The residue was subsequently diluted with distilled water to obtain a viscous extract before use.

Flavonoid content of *S. zalacca* ethanolic extract

Flavonoids were measured quantitatively and qualitatively. 1 mg of ESP was mixed with two drops of $FeCl_3$ for a qualitative test. A green-to-yellow-green color was used to indicate the presence of flavonoid compounds in the sample (Darmayuda et al., 2021). Total flavonoid content (TFC) of the extract was quantified by the aluminum chloride ($AlCl_3$) colorimetric method using quercetin as a standard, expressed as mg quercetin equivalents per g extract (mg QE/g) (Chang et al., 2002), with slight modifications. A quercetin standard (Sigma, USA) was diluted to 10 concentrations (10 –100 µg/mL) in 96% ethanol. 0.5 mL of ESP and quercetin were mixed with 1.5 mL of ethanol, 0.1 mL of $AlCl_3$ 10% (Merck, Germany), 0.1 mL of potassium acetate, and 2.8 mL of distilled water. The absorbance was measured in triplicate using a UV-visible spectrophotometer (Thermo Fisher Scientific, USA) (415 nm). The linear regression equation was created based on the quercetin standard (10–100 µg/mL) after subtraction of the reagent blank. TFC was determined based on the calibration curve, which was linear ($y = 0.016x + 0.0001$, $R^2 = 0.9988$).

Experimental animals

The research was conducted at the Center for Food and Nutrition Studies of Gadjah Mada University in Yogyakarta for 25 days. The approval by the Medical Research Bioethics Commission, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang No.524/XII/2022/Komisi Bioetik was obtained on 30th December 2022. All animal procedures were conducted in accordance with institutional guidelines and are reported in compliance with the ARRIVE guidelines 2.0 (du Sert et al., 2020). Those procedures were non-invasive and did not cause pain or distress to the animals; therefore, anesthesia was not required according to institutional guidelines. Animals were monitored after sampling for signs of distress or ocular injury. Humane endpoints included persistent lethargy, body weight loss exceeding 15% of baseline, or signs of severe distress.

Study design

A total of 30 male Wistar rats aged 3 months (body weights: 190-210 g) were assigned to 5 groups by random allocation. The animals were housed in standard polypropylene cages under controlled conditions (25 ± 2°C, 50–60% humidity, 12 h light/dark cycle). Rats were housed under identical, standardized conditions to minimize environmental bias. They were acclimatized for one week prior to the experiment, during which they were fed a standard pellet diet and water *ad libitum*. Chicken liver juice (CL) was administered orally using a feeding tube at a dose of 8 g/200 g BW, homogenized in 4 mL distilled water, once daily for 10 consecutive days (days 8–17) to induce hyperuricemia. The administered volume was adjusted according to animal body weight to ensure accurate dosing. Hyperuricemia was induced by oral administration of chicken liver juice, a purine-rich preparation that has been used in rodent studies to elevate serum uric acid levels (Karyadi et al., 2023). The effectiveness of chicken liver juice as an inducer of hyperuricemia, comparable to potassium oxonate, has been demonstrated in previous work (Wikantyasning et al., 2024). Group 1 served as the normal control consisting of animals that were administered with water intragastrically; Group 2 as the hyperuricemia control; Group 3 was induced in combination of CL and allopurinol (9 mg/kg BW); Groups 4 and 5 were induced with CL and given ESP at doses of 210 and 420 mg/kg BW, respectively. The allopurinol dose (9 mg/kg BW) was selected based on published hyperuricemia models, which used approximately 10 mg/kg BW as a reference dose (An et al., 2023). These doses are based on previous studies demonstrating significant reductions in serum uric acid and oxidative stress markers at comparable mg/kg levels in Wistar rats (Pertiwi et al., 2025). Serum uric acid levels were measured at the end of induction as pre-test values. From day 18 to day 24, chicken liver administration was discontinued, and it was continued for seven days. Post-test serum uric acid levels were measured at the end of the treatment period, and the change in uric acid levels between pre- and post-test was analyzed statistically (day 24). The details of the experimental timeline and group allocation are summarized in Fig. 1.

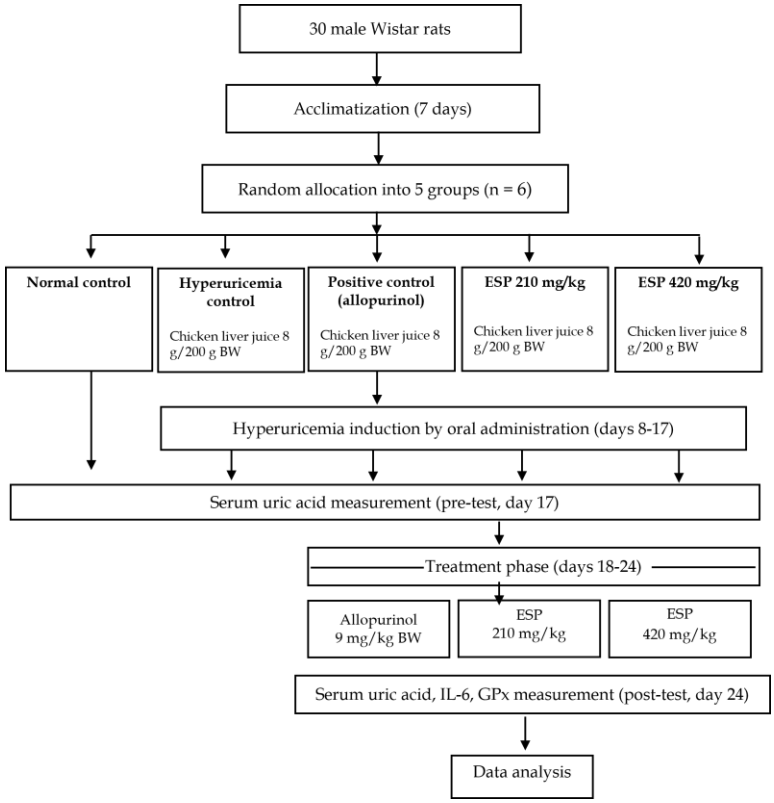


Figure 1. Experimental timeline of hyperuricemia induction and treatment in rats.

After acclimatization, hyperuricemia was induced using chicken liver juice for 10 days, followed by seven days of allopurinol or ESP treatment and biochemical assessment.

Laboratory test

Laboratory analyses were conducted using coded samples to blind investigators to group allocation. Uric acid levels were assessed pre- and post-treatment administration of ESP extract and allopurinol. A blood sample of 3 mL was collected by inserting a hematocrit pipette into the orbital sinus of rats via the ophthalmic vein (Donovan & Brown, 2005). A uricase quantified serum uric acid–peroxidase colorimetric method kit (Infinity™ Uric Acid Liquid Stable Reagent (Fisher Diagnostics, Thermo Fisher Scientific, USA; Cat. No. TR24321), with absorbance read at 520 nm per the manufacturer's instructions.

The serum was extracted and measured with a spectrophotometer UV-Vis (Thermo Fisher Scientific, USA) (520 nm). The measurement was conducted using the Uricase method with Lipid Clearing Factor (LCF) (Fossati et al., 1980).

The IL-6 and GPx measurements were carried out after ESP and allopurinol treatment. Blood samples were taken, and 0.2 mL serum was extracted. Serum interleukin-6 (IL-6) levels were quantified using a rat IL-6 sandwich ELISA assay kit (Elabscience, USA; Cat. No. E-EL-R0015) within a detection range of 12.5–800 pg/mL, with reported intra- and inter-assay coefficients of variation of <10% and <12%, respectively. Serum samples were diluted as required to fall within the linear range of the standard curve, and absorbance was measured using an ELISA reader (Thermo Fisher Scientific, USA) (450 nm). GPx protein levels in rat serum were determined using a commercially available rat GPx1 ELISA kit (Elabscience, Cat. No. E-EL-R2491), according to the manufacturer's instructions. The assay has a detection range of 31.25–2000 pg/mL and a sensitivity of 18.75 pg/mL. Serum samples were diluted as required to fall within the linear range of the standard curve. Absorbance was measured at 450 nm using a microplate reader, and GPx concentrations were calculated from a standard curve generated with recombinant standards.

Statistical analysis

The data analysis was done using SPSS version 26.0 for Windows (IBM Corp., Armonk, New York, USA). Serum uric acid levels were analyzed using analysis of covariance (ANCOVA), with post-treatment uric acid as the dependent variable, treatment group as the fixed factor, and baseline uric acid as the covariate. Multiple comparisons were conducted using the Bonferroni adjustment. The data on the reduction in uric acid, IL-6, and GPx were assessed for normality and homogeneity using the Shapiro-Wilk and Levene tests. One-way

ANOVA was used to analyze IL-6 and GPx data, followed by the post hoc Tukey test.

RESULTS

Total flavonoid content of ethanol extract of *S. zalacca* peel

Quantitative analysis showed that ESP contained 43.3 mg QE/g extract (Fig. 2). During qualitative assessment, a green-to-greenish-yellow coloration was observed, supporting the presence of flavonoid constituents in the extract.

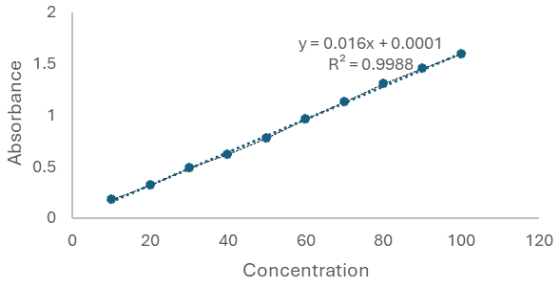


Figure 2. Quercetin standard curve used for the determination of total flavonoid content.

Absorbance was measured at 415 nm over the linear concentration range of 10–100 µg/mL. Total flavonoid content of the extract was calculated from this regression and expressed as mg quercetin equivalents per g extract (mg QE/g). X-axis: Concentration (µg/mL). Y-axis: Absorbance at 415 nm. $y = 0.016x + 0.0001$, $R^2 = 0.9988$.

Analysis of mean serum uric acid levels pre- and post-intervention

Hyperuricemia was successfully induced, as evidenced by a rise in mean pre-treatment serum uric acid from 1.75 ± 0.16 mg/dL (normal control) to 8.37 ± 0.24 mg/dL (hyperuricemia control) ($p<0.001$). ESP administration produced dose-dependent reductions in serum uric acid: post-treatment means were 3.03 ± 0.14 mg/dL (210 mg/kg) and 2.22 ± 0.06 mg/dL (420 mg/kg), respectively, compared with 3.01 ± 0.18 mg/dL in the allopurinol group (Table 1).

The mean serum uric acid level in group 1 (1.75 ± 0.16 mg/dL) served as a reference. Group 2 (8.37 ± 0.24 mg/dL) confirmed successful induction of hyperuricemia. Group 3, which received allopurinol, demonstrated a significant decline in uric acid levels (5.03 ± 0.06 mg/dL) after treatment.

Baseline (pre-treatment) serum uric acid levels differed markedly between groups, confirming successful induction of hyperuricemia. The CL-induced group exhibited a substantial increase in pre-treatment serum uric acid compared with the normal control ($p<0.001$). Following treatment, serum uric acid levels decreased in the allopurinol and ESP treatment groups.

ANCOVA demonstrated a significant effect of treatment on post-treatment serum uric acid levels after adjustment for baseline UA ($F(4,24) = 13827.3$, $p<0.001$), with a very large effect size (partial $\eta^2 = 1.000$). A dose-dependent response was observed. ESP 420 mg/kg BW produced the largest decrease in uric acid and IL-6 and the greatest increase in GPx versus hyperuricemia controls ($p<0.001$). The 210 mg/kg dose showed intermediate effects (Table 2).

Analysis of mean serum IL-6 and GPx levels post-treatment

IL-6 concentrations were significantly elevated in hyperuricemic rats (79.62 ± 0.92 pg/mL). One-way ANOVA revealed a significant difference among groups ($p<0.001$), indicating a substantial effect of treatments on IL-6 levels. Allopurinol reduced mean IL-6 levels (60.64 ± 1.17 pg/mL), whereas ESP produced a clear dose-dependent reduction. The higher ESP dose (420 mg/kg BW) resulted in significantly lower IL-6 levels post-treatment (32.96 ± 1.51 pg/mL; 95% CI 31.38-34.54) than the 210 mg/kg BW dose (49.01 ± 1.48 pg/mL) (Table 3). The post hoc Tukey test results for IL-6 levels among the experimental groups showed significant differences ($p<0.001$) between all pairwise comparisons, indicating that each treatment group exhibited distinct IL-6 levels. These findings suggest that the interventions had a pronounced impact on IL-6 activity. Tukey analysis confirmed significant differences among all experimental groups for IL-6 ($p<0.05$), indicating a large treatment effect ($\eta^2 = 0.997$).

GPx protein levels were significantly decreased by hyperuricemia and were restored by treatment; the highest ESP dose yielded GPx protein levels greater than those observed in normal controls (one-way ANOVA, $p<0.001$). ESP administration enhanced GPx protein levels in a dose-dependent manner, with the highest levels observed at 420 mg/kg BW (51.19 ± 0.72 pg/mL; 95% CI 50.43-51.94 pg/mL). Post-hoc Tukey analysis confirmed significant differences among all experimental groups for GPx protein levels ($p<0.05$), indicating a large treatment effect ($\eta^2 = 0.995$) (Table 4).

Table 1. Uric acid levels on pre-test and post-test, and the reduction in uric acid levels due to the administration of *S. zalacca* peel ethanol extract.

Group	Mean uric acid levels (mg/dL)		Δ Uric acid level (mg/dL)
	Pre-test	Post-test	
Group 1	1.65 ± 0.15	1.75 ± 0.16	-0.10 ± 0.02
Group 2	8.07 ± 0.24	8.37 ± 0.24	-0.30 ± 0.02
Group 3	8.04 ± 0.23	3.01 ± 0.18	5.03 ± 0.06
Group 4	8.03 ± 0.18	3.03 ± 0.14	5.00 ± 0.05
Group 5	8.01 ± 0.14	2.22 ± 0.06	5.78 ± 0.10

Results represent mean ± SD (n = 6). Δ = pre-test − post-test. Group 1: Normal control; Group 2: Hyperuricemia control induced by chicken liver juice (CL) 8 g/200 g BW; Group 3: CL and allopurinol (9 mg/kg BW); Group 4: CL and *S. zalacca* ethanolic extract (ESP) 210 mg/kg BW; and Group 5: CL and ESP 420 mg/kg BW).

Table 2. Effects of ESP on serum uric acid levels in hyperuricemic rats (ANCOVA results).

Group	Serum UA pre-test (mean ± SD) (mg/dL)	Serum UA post-test* (adjusted mean ± SE) (mg/dL)	p-value**
Group 1	1.65 ± 0.15	5.90 ± 0.26	0.003
Group 2	8.07 ± 0.25	7.31 ± 0.07	Reference
Group 3	8.04 ± 0.24	1.97 ± 0.07	<0.001
Group 4	8.03 ± 0.19	2.00 ± 0.07	<0.001
Group 5	8.01 ± 0.15	1.21 ± 0.07	<0.001

*Post-test UA values represent estimated marginal means adjusted for baseline UA using ANCOVA. ** p-values indicate Bonferroni-adjusted pairwise comparisons versus the CL-induced group. Sample size (n = 6). ANCOVA model: post-treatment UA = treatment group + baseline UA. Overall model: ($F(4,24) = 13827.3$, $p<0.001$, $R^2 = 1.000$). Group 1: Normal control; Group 2: Hyperuricemia control induced by chicken liver juice (CL) 8 g/200 g BW; Group 3: CL and allopurinol (9 mg/kg BW); Group 4: CL and *S. zalacca* ethanolic extract (ESP) 210 mg/kg BW; and Group 5: CL and ESP 420 mg/kg BW). UA: Uric acid.

Table 3. Post-treatment IL-6 concentrations.

Group	IL-6 (pg/mL)	One-way ANOVA	95% CI	
			Lower bound	Upper bound
Group 1	26.27 ± 0.48^{a}		25.76	26.78
Group 2	79.62 ± 0.92^{e}		78.65	80.58
Group 3	60.64 ± 1.17^{d}	$p<0.001$*	59.41	61.88
Group 4	49.01 ± 1.48^{c}		47.46	50.56
Group 5	32.96 ± 1.51^{b}		31.38	34.54

Results represent mean ± SD (n = 6). One-way ANOVA across groups: IL-6 $F[4,25]= 2001.24$, $p<0.001$, $\eta^2 = 0.997$. *Statistically significant differences ($p<0.05$). Different superscript letters indicate significant differences (Post Hoc Tukey, $p<0.05$). Group 1: Normal control; Group 2: Hyperuricemia control induced by chicken liver juice (CL) 8 g/200 g BW; Group 3: CL and allopurinol (9 mg/kg BW); Group 4: CL and *S. zalacca* ethanolic extract (ESP) 210 mg/kg BW; and Group 5: CL and ESP 420 mg/kg BW). CI: Confidence interval.

Table 4. Post-treatment GPx protein levels.

Group	GPx protein level (pg/mL)	One-way ANOVA	95% CI	
			Lower bound	Upper bound
Group 1	55.83 ± 0.36[e]		55.45	56.21
Group 2	31.32 ± 0.71[a]		30.57	32.06
Group 3	47.92 ± 0.73[c]	p<0.001*	47.15	48.68
Group 4	45.97 ± 0.58[b]		45.36	46.58
Group 5	51.19 ± 0.72[d]		50.43	51.94

Results represent mean ± SD (n = 6). One-way ANOVA across groups: GPx $F[4,25]= 1271.84$, $p<0.001$, $\eta^2 = 0.995$. Post-hoc Tukey $p<0.05$. Group 1: Normal control; Group 2: Hyperuricemia control induced by chicken liver juice (CL) 8 g/200 g BW; Group 3: CL and allopurinol (9 mg/kg BW); Group 4: CL and *S. zalacca* ethanolic extract (ESP) 210 mg/kg BW; and Group 5: CL and ESP 420 mg/kg BW). CI: Confidence interval.

DISCUSSION

The present results indicate that ESP reduced serum uric acid and systemic inflammation while augmenting antioxidant enzyme activity in a rat model of hyperuricemia. The observed antihyperuricemic effect may be attributable to flavonoid constituents present in the peel extract, which have been reported to inhibit XO *in vitro*. However, direct measurements of XO activity and phytochemical identification were not performed in this study; therefore, the mechanistic interpretation remains provisional. Additional experiments (XO inhibition assay, urinary uric acid measurement, and phytochemical profiling) are recommended to substantiate a specific mechanism.

Elevated UA levels lead to higher oxidative stress and inflammation. Serum uric acid levels increased in hyperuricemia. ESP treatment significantly reduced uric acid levels at doses of 210 mg/kg BW and 420 mg/kg BW, induced by CL. These findings aligned with those of Priyatno et al. (2012), who reported a reduction in serum uric acid levels after administering the ethanolic extract of *S. zalacca* var. bongkok at a dose of 200 mg/kg BW. While ESP improved all biomarkers, direct superiority over allopurinol cannot be concluded without an analysis powered for between-treatment contrasts and accounting for effect sizes. Some flavonoids, such as diosmetin and luteolin, have shown potent XO inhibition *in vitro*; however, these findings cannot be directly compared with allopurinol's *in vivo* efficacy (Nile et al., 2018).

Flavonoids are widely reported to modulate uric acid metabolism by inhibiting XO and attenuating oxidative stress, as well as by affecting renal urate handling. Preclinical reviews and animal studies indicate that flavonoid compounds can interact with XO and modulate the expression or activity of urate transport proteins, thereby promoting uric acid excretion and reducing oxidative stress *in vivo* (Liu et al., 2024). However, extrapolation to mechanistic efficacy in the current model requires caution. In the absence of direct XO activity assays, urinary uric acid measurements, or evaluation of renal urate transporters (e.g., URAT1, GLUT9) in this study, the present data do not allow definitive conclusions regarding the precise pathways underlying the urate-lowering effect of ESP.

Inflammation plays a central role in the pathophysiology of hyperuricemia, with IL-6 acting as a key mediator linking urate accumulation, oxidative stress, and tissue injury (Zhou et al., 2018). In the present study, ESP significantly reduced serum IL-6 levels in a dose-dependent manner, indicating attenuation of systemic inflammation in hyperuricemic rats. Elevated uric acid levels, including crystal deposition, are known to promote inflammatory responses by increasing cytokine production, such as IL-6 and IL-8, even in the absence of overt gout symptoms (Liu et al., 2021). The reduction in IL-6 observed following ESP administration is consistent with reports that phenolic- and flavonoid-rich compounds can modulate inflammatory and oxidative processes associated with uric acid metabolism. Recent evidence indicates that several phenolic compounds interact with xanthine oxidase and modulate pathways associated with urate-associated inflammation (Mehmood et al., 2022). Nevertheless, because inflammatory signaling pathways such as NF-κB activation were not directly examined in this study, these mechanisms should be regarded as contextual interpretations rather than confirmed modes of action.

Oxidative stress was further evaluated through GPx protein levels, which were significantly reduced in untreated hyperuricemic rats, confirming impairment of endogenous antioxidant defenses. ESP administration effectively restored GPx protein levels in a dose-dependent manner, with the higher dose normalizing GPx values toward those of the control group. Although changes in GPx protein concentration do not directly represent enzymatic activity, alterations in GPx protein abundance have been interpreted in preclinical studies as part of an integrated antioxidant defense response. In a rat model of oxidative challenge,

Ścibior et al. (2021) demonstrated that GPx protein levels positively correlated with other antioxidant proteins (GST, GR, GCLC) and with Nrf2, supporting the interpretation that GPx protein expression reflects coordinated redox regulation rather than isolated enzyme kinetics. Consistent with these observations, the restoration of GPx protein levels following ESP treatment in the present study suggests enhancement of endogenous antioxidant defense capacity under hyperuricemia conditions. However, direct assessment of upstream regulatory pathways, including Nrf2 signaling, was beyond the scope of this study and warrants further investigation.

This study has several limitations. Hyperuricemia was induced using a dietary high-purine model rather than a potassium oxonate model, which may involve different mechanisms. The sample size per group was relatively small. Renal function parameters (blood urea nitrogen and creatinine), urinary uric acid excretion, and histopathological analysis were not performed. In addition, XO activity and inflammatory signaling pathways were not directly measured; therefore, mechanistic interpretations remain inferential and warrant confirmation in future studies.

CONCLUSION

Ethanolic *Salacca zalacca* peel extract reduced serum uric acid and IL-6 and increased GPx activity in rats with diet-induced hyperuricemia, with the 420 mg/kg dose showing the largest effects; further mechanistic and safety studies are warranted. These findings indicate that ESP may help restore the balance between inflammation and antioxidants in hyperuricemia. Therefore, ESP may be considered a potential natural adjuvant in the management of hyperuricemia. Further studies are needed to elucidate the underlying mechanisms, incorporating targeted enzymatic and signaling analyses.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

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GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors used ChatGPT (OpenAI) to improve the language and readability of the manuscript. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools.

DATA AVAILABILITY

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

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AUTHOR CONTRIBUTION:

Contribution	Pertiwi D	Puspaningrum DK	Mardhiani FA
Concepts or ideas	x		
Design	x		
Definition of intellectual content	x		
Literature search	x		x
Experimental studies	x	x	
Data acquisition	x	x	
Data analysis	x		x
Statistical analysis	x		x
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
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