



Antihyperuricemic effect of ethanol extract of *Erythrina subumbrans* (Hassk.) Merr. leaves in a fructose-potassium oxonate-induced male Wistar rat model

[Efecto antihiperuricémico del extracto etanólico de hojas de *Erythrina subumbrans* (Hassk.) Merr. en un modelo de rata Wistar macho inducido por fructosa-oxonato de potasio]

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Abstract

Context: Hyperuricemia is associated with gout, oxidative stress, and renal and hepatic dysfunction. *Erythrina subumbrans* (Hassk.) Merr. contains bioactive metabolites, but its antihyperuricemic activity remains insufficiently evaluated.

Aims: To evaluate the antihyperuricemic activity of the ethanol extract of *E. subumbrans* leaves *in vitro* and in a fructose-potassium oxonate-induced hyperuricemic rat model.

Methods: Xanthine oxidase inhibition was assessed colorimetrically. Male Wistar rats were assigned to normal control, negative control, allopurinol, and extract-treated groups (100, 200, and 400 mg/kg body weight) in a preventive/co-treatment design. Serum uric acid, creatinine, aminotransferases, and malondialdehyde were measured and analyzed using repeated measures analysis. Liver and kidney tissues were examined histologically.

Results: The ethanol extract of *E. subumbrans* leaves inhibited xanthine oxidase *in vitro*, with a 50% inhibitory concentration of 30.98 ± 0.64 µg/mL, indicating lower activity than allopurinol (1.24 ± 0.64 µg/mL). At day 60, the extract at 100, 200, and 400 mg/kg attenuated serum uric acid levels to 3.28 ± 0.14 , 3.26 ± 0.19 , and 2.64 ± 0.09 mg/dL, respectively, compared with the negative control group ($p < 0.05$). Lower creatinine, aminotransferase, and malondialdehyde values were observed in the extract-treated groups than in the negative control group. Histopathological alterations of the liver and kidney were numerically reduced, although not all pairwise comparisons reached statistical significance.

Conclusions: The ethanol extract of *E. subumbrans* leaves showed antihyperuricemic activity in this preventive/co-treatment model. The observed effect may have been partly related to xanthine oxidase inhibition; however, further mechanistic, standardization, and safety studies are required.

Keywords: alanine aminotransferase; creatinine; hyperuricemia; malondialdehyde; rats, Wistar; uric acid.

Resumen

Contexto: La hiperuricemia se asocia con gota, estrés oxidativo y disfunción renal y hepática. *Erythrina subumbrans* (Hassk.) Merr. contiene metabolitos bioactivos, pero su actividad antihiperuricémica aún no ha sido suficientemente evaluada.

Objetivos: Evaluar la actividad antihiperuricémica del extracto etanólico de hojas de *E. subumbrans* *in vitro* y en un modelo de ratas hiperuricémicas inducido por fructosa-oxonato de potasio.

Métodos: La inhibición de la xantina oxidasa se evaluó mediante un ensayo colorimétrico. Ratas Wistar macho fueron distribuidas en grupos control normal, control negativo, alopurinol y grupos tratados con extracto a dosis de 100, 200 y 400 mg/kg de peso corporal, en un diseño preventivo/cotratamiento. Se midieron ácido úrico sérico, creatinina, aspartato aminotransferasa, alanina aminotransferasa y malondialdehído, y se analizaron mediante análisis de medidas repetidas. Los tejidos hepático y renal fueron examinados histológicamente.

Resultados: El extracto etanólico de hojas de *E. subumbrans* inhibió la xantina oxidasa *in vitro*, con una concentración inhibitoria del 50% de $30,98 \pm 0,64$ µg/mL, mostrando menor actividad que el alopurinol ($1,24 \pm 0,64$ µg/mL). En el día 60, el extracto a 100, 200 y 400 mg/kg atenuó los niveles séricos de ácido úrico a $3,28 \pm 0,14$; $3,26 \pm 0,19$; y $2,64 \pm 0,09$ mg/dL, respectivamente, en comparación con el grupo control negativo ($p < 0,05$). Se observaron valores más bajos de creatinina, aminotransferasas y malondialdehído en los grupos tratados con extracto que en el grupo control negativo. Las alteraciones histopatológicas hepáticas y renales se redujeron numéricamente, aunque no todas las comparaciones por pares alcanzaron significancia estadística.

Conclusiones: El extracto etanólico de hojas de *E. subumbrans* mostró actividad antihiperuricémica en este modelo preventivo/cotratamiento. El efecto observado puede haber estado parcialmente relacionado con la inhibición de la xantina oxidasa; sin embargo, se requieren estudios mecanísticos, de estandarización y de seguridad adicionales.

Palabras Clave: ácido úrico; alanina aminotransferasa; creatinina; hiperuricemia; malondialdehído; ratas Wistar.

ARTICLE INFO

Received: November 15, 2025.

Accepted: June 15, 2026.

Available Online: June 17, 2026.

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Abbreviations: ALT/SGPT: alanine aminotransferase/serum glutamic-pyruvic transaminase; AST/SGOT: aspartate aminotransferase/serum glutamic-oxaloacetic transaminase; BW: body weight; EES: ethanol extract of *Erythrina subumbrans*; H&E: hematoxylin and eosin; MDA: malondialdehyde; Na-CMC: sodium carboxymethyl cellulose; XO: xanthine oxidase.

INTRODUCTION

Hyperuricemia is a condition characterized by elevated serum uric acid levels and has become a significant public health concern worldwide. Excessive sugar consumption, particularly from sweetened beverages and processed foods, has been associated with an increased risk of hyperuricemia, gout, and other metabolic disorders (Caliceti et al., 2017; Timsans et al., 2024). Fructose increases uric acid production through hepatic metabolism by accelerating the degradation of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), a precursor of uric acid (Zhang et al., 2022). This process enhances purine metabolism and may contribute to uric acid accumulation and gout development (Lubawy & Formanowicz, 2023). Serum uric acid reference intervals vary according to sex, age, population, and laboratory methods; however, laboratory reference ranges of approximately 3.5–7.7 mg/dL in males and 2.6–6.0 mg/dL in females have been reported in healthy adults (Das et al., 2014).

The global burden of hyperuricemia and gout has increased in recent years and varies across populations. Gout prevalence has been reported to range from <1% to 6.8%, with an incidence of 0.58–2.89 per 1000 person-years. It is more common in men, older adults, and individuals with metabolic comorbidities (Dehlin et al., 2020). This increasing burden is associated with lifestyle-related and metabolic risk factors, including high-purine and fructose-rich diets, alcohol consumption, obesity, hypertension, and metabolic syndrome (Dehlin et al., 2020; Du et al., 2024). In Indonesia, national epidemiological data on gout remain limited; therefore, joint disease data should be interpreted with caution. The Indonesian Basic Health Research 2018 reported that the prevalence of physician-diagnosed joint disease among individuals aged ≥15 years was 7.30% nationally, with higher proportions reported in Aceh (13.26%), Bengkulu (12.11%), Bali (10.46%), and Papua (10.43%) (National Institute of Health Research and Development, 2019).

Conventional therapies, such as allopurinol, are effective in lowering uric acid levels. However, long-term use of these drugs may cause adverse effects, including gastrointestinal disorders and hypersensitivity reactions (Qurie et al., 2023). Therefore, the identification of safe and effective natural agents for hyperuricemia remains of pharmacological interest (Abdel Mageed et al., 2025). One Indonesian medicinal plant, locally known as dadap serep, is *Erythrina subumbrans* (Hassk.) Merr. (*Fabaceae*). *E. subumbrans* has been traditionally used to treat postpartum fever, prevent

miscarriage, treat internal wounds and stomach pain, stimulate breast milk production, and as an antimalarial, antimicrobial, antioxidant, and anti-inflammatory agent (Phukhatmuen et al., 2021). Previous studies have reported that *E. subumbrans* contains bioactive secondary metabolites, particularly flavonoids, polyphenols, and other phenolic compounds, which may contribute to antioxidant and enzyme-inhibitory activities (Phukhatmuen et al., 2021; Susilawati et al., 2024). Since xanthine oxidase plays a key role in uric acid production, and several plant-derived flavonoids have been reported to exert antihyperuricemic effects through xanthine oxidase inhibition and modulation of urate handling, EES was considered a potential candidate for antihyperuricemic evaluation (An et al., 2023; Liu et al., 2021).

Accordingly, this study evaluated the antihyperuricemic activity of the ethanol extract of *E. subumbrans* leaves (EES) in a fructose-potassium oxonate-induced hyperuricemic rat model. In addition to serum uric acid, biochemical markers related to renal function, liver function, and oxidative stress, including creatinine, AST/SGOT, ALT/SGPT, and malondialdehyde (MDA), were measured (Ayala et al., 2014; Ejaz et al., 2020; Liu et al., 2021). Liver and kidney histopathological changes were also evaluated to determine whether the urate-lowering effect was accompanied by attenuation of tissue alterations. Because the extract contained several classes of secondary metabolites, xanthine oxidase inhibition and attenuation of lipid peroxidation were considered possible mechanisms to be explored (Phukhatmuen et al., 2021; Susilawati et al., 2024).

MATERIAL AND METHODS

Materials and reagents

Animal feed (standard pellet diet, local certified supplier, Bandung, Indonesia), fructose powder (PT ROFA Laboratorium Indonesia, Bandung, Indonesia), potassium oxonate, xanthine oxidase, xanthine substrate, and phosphate buffer (Sigma-Aldrich, St. Louis, MO, USA), uric acid reagent (BioMaxima S.A., Lublin, Poland), creatinine reagent, AST/SGOT reagent, and ALT/SGPT reagent (Reiged Diagnostics/PT Rajaerba Indochem, Tangerang Selatan, Indonesia), tetraethoxypropane (Sigma-Aldrich, St. Louis, MO, USA), thio-barbituric acid, trichloroacetic acid, concentrated hydrochloric acid, and sodium hydroxide (Merck KGaA, Darmstadt, Germany), allopurinol tablets 100 mg (Novapharin Pharmaceutical Industries, Gresik, Indonesia), 0.5% sodium carboxymethyl cellulose (Na-

CMC), 96% ethanol, 1% ferric chloride, chloroform, ammonium hydroxide, Mayer's reagent, sulfuric acid, magnesium powder, diethyl ether, and Liebermann-Burchard reagent were used in this study. Unless otherwise stated, the remaining chemicals were of analytical grade and were obtained from certified chemical suppliers in Indonesia.

Plant material, extract preparation, and phytochemical screening

Fresh leaves of *E. subumbrans* were collected from Kampung Kamal, Tanjungmedar District, Sumedang Regency, West Java, Indonesia (GPS coordinates: 6.71333, 107.88611), in January 2025. The plant material was taxonomically authenticated at Herbarium Jatinangor, Plant Taxonomy Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Indonesia, and was identified as *Erythrina subumbrans* (Hassk.) Merr., family *Fabaceae*. The plant identification document was issued under No. 33/HB/01/2025, and the authenticated reference specimen was preserved at Herbarium Jatinangor for future reference.

The collected leaves were washed, cut into small pieces, and dried in an oven at 50–60°C until a constant weight was obtained. The dried leaves were then ground into coarse powder. Extraction was performed by maceration using 96% ethanol for three days with occasional stirring. The filtrate was collected and concentrated using a rotary evaporator to obtain a viscous ethanol extract of *E. subumbrans* leaves, hereafter referred to as EES. The extraction yield was 19.34% w/w. Qualitative phytochemical screening was performed only as a preliminary characterization of EES and indicated the presence of flavonoids, alkaloids, saponins, tannins, and steroids.

Xanthine oxidase (XO) inhibition assay

The XO inhibitory activity of EES was assessed using the Xanthine Oxidase Inhibitor Screening Kit (Elabscience Biotechnology Co., Ltd., Wuhan, China; Cat. No. E-BC-D019) in a 96-well microplate reader. The detection principle of this kit is based on XO-mediated conversion of the substrate to form a colored product with maximum absorbance at 560 nm. In the presence of an inhibitor, the color intensity decreases in proportion to the degree of XO inhibition. EES and allopurinol were tested at serial concentrations prepared in phosphate buffer (pH 7.5).

Briefly, 115 µL of phosphate buffer (pH 7.5) was added to each well for the blank control. The enzyme control consisted of 85 µL of phosphate buffer and 30 µL of XO solution. For the sample blank, 50 µL of sample solution was mixed with 65 µL of phosphate buffer.

For the sample reaction, 50 µL of EES solution was mixed with 35 µL of phosphate buffer and 30 µL of XO solution. Allopurinol was used as the reference XO inhibitor and was prepared in the same manner as the sample reaction. After incubation at 25°C for 15 min, xanthine substrate solution was added and the mixture was incubated at 30°C for 30 min. The reaction was terminated by adding 20 µL of 1 mol/L HCl, and absorbance was measured at 560 nm.

The percentage of XO inhibition was calculated relative to the enzyme control using the formula [1] (Dhammaraj et al., 2024).

$$\text{Inhibition (\%)} = \frac{(A_{\text{control}} - A_{\text{sample}})}{A_{\text{control}}} \times 100 \quad [1]$$

Where A_{control} is the control absorbance, and A_{sample} is the absorbance of the sample (EES).

The IC_{50} value was obtained from the concentration-response curve using regression analysis. All measurements were performed in triplicate, and IC_{50} values were expressed as mean $\pm$ SD.

Animal handling and experimental design

Animal handling procedures were approved by the Research Ethics Committee of Universitas Padjadjaran, Bandung, Indonesia (<https://kep.unpad.ac.id/>) with approval document No. 426/UN6.KEP/EC/2025, registration No. 2502020153, and all procedures were in accordance with the 3Rs (Replacement, Reduction, Refinement) and 5Fs (Freedom from Hunger and Thirst, Freedom from Discomfort, Freedom from Pain, Injury, and Disease, Freedom to Express Normal Behaviour, and Freedom from Fear and Distress) animal welfare principles.

Male Wistar rats aged 6–8 weeks and weighing 200–250 g were obtained from a certified breeder (Barokah, Bandung, Indonesia). The animals were acclimatized for 7 days before the experiment under standard laboratory conditions at 22–25°C, 50–60% relative humidity, and a 12 h light/dark cycle, with free access to standard pellet food and water.

After acclimatization, the rats were randomly allocated into six groups ($n = 4$ per group) using a computer-generated sequence. The sample size was determined based on a preliminary experimental design, and no formal a priori power calculation was performed. The study was conducted for 60 days using a preventive/co-treatment design. Fructose was administered by oral gavage as a 60% w/v solution at 2.5 mL/200 g BW/day, equivalent to 12.5 mL/kg BW/day or 7.5 g/kg BW/day, for 60 consecutive days. Potassium oxonate was suspended in 0.5% Na-CMC and administered orally at 1.0 g/kg BW once daily from day 50 to day 60. Allopurinol was suspended in 0.5% Na-

CMC and administered orally at 100 mg/kg BW once daily for 60 days. EES was suspended in 0.5% Na-CMC and administered orally at 100, 200, or 400 mg/kg BW once daily for 60 days.

The experimental groups were as follows:

Group 1: normal control group, administered 0.5% Na-CMC.

Group 2: negative control group, administered fructose and potassium oxonate without treatment.

Group 3: allopurinol-treated group, administered fructose, potassium oxonate, and allopurinol.

Group 4: EES 100 mg/kg BW group, administered fructose, potassium oxonate, and EES 100 mg/kg BW.

Group 5: EES 200 mg/kg BW group, administered fructose, potassium oxonate, and EES 200 mg/kg BW.

Group 6: EES 400 mg/kg BW group, administered fructose, potassium oxonate, and EES 400 mg/kg BW.

Before blood collection, food was withheld for 8 h, while water remained available ad libitum. Blood samples were collected at baseline (D0) and at the end of the experimental period (D60). The D0 blood collection was performed as survival sampling because the animals were maintained in the study until D60, whereas the D60 collection was conducted as terminal sampling before euthanasia and tissue collection. The ethics review documents associated with the same registration number specifically included clarification of the blood collection route and CO₂ anesthesia procedure. For D0 survival sampling, rats were anesthetized by exposure to CO₂ at <30% of the chamber volume per minute for less than 1 min to minimize pain and distress during blood collection, as described in the institutional ethics review documents. Blood was then collected from the orbital sinus/plexus using a capillary tube inserted through the medial canthus of the eye. This procedure was consistent with a previous experimental report in which brief CO₂ exposure was followed by retro-orbital blood sampling in rats (Zardooz et al., 2010); however, the citation was used only as a supporting experimental reference, whereas the present procedure followed the approved institutional ethics documents. The orbital sinus/plexus route was selected because sufficient serum volume was required for multiple biochemical measurements from the same animals, including serum uric acid, creatinine, AST/SGOT, ALT/SGPT, and MDA. This approach was used to optimize sample collection and avoid repeated blood sampling. No topical ophthalmic anesthetic or ocular lubricant was applied during the procedure. To avoid repeated sampling from the same eye, blood was collected from the left orbital sinus at D0 and from the right orbital sinus at D60 in the same animals.

Approximately 0.5–1.0 mL of blood was collected into Eppendorf tubes for biochemical analysis. After D0 blood collection, animals were monitored until recovery from anesthesia, including respiration, recovery of activity, bleeding at the sampling site, ocular condition, signs of distress, and general behavior. All animals recovered after D0 blood collection and were considered suitable to continue the experimental protocol until D60. At D60, terminal blood collection was followed by euthanasia using CO₂ anesthesia at a flow rate of 30–70% of the chamber volume per minute. Liver and kidney tissues were then collected and processed for histopathological examination using hematoxylin and eosin (H&E) staining.

Biochemical analysis

Serum uric acid was measured using a uric acid reagent kit (BioMaxima S.A., Lublin, Poland) according to the manufacturer's instructions. Serum creatinine, AST/SGOT, and ALT/SGPT levels were measured enzymatically using a Microlab 300 analyzer (Vital Scientific B.V., Dieren, The Netherlands). For AST/SGOT and ALT/SGPT analysis, 100 µL of serum was mixed with 500 µL of AST/SGOT or ALT/SGPT monoreagent (Reiged Diagnostics/PT Rajaerba Indochem, Tangerang Selatan, Indonesia), incubated for 1 min at 37°C, and measured at 340 nm (Bajaj et al., 2024). For creatinine measurement, 50 µL of serum was mixed with 500 µL of creatinine monoreagent (Reiged Diagnostics/PT Rajaerba Indochem, Tangerang Selatan, Indonesia), incubated for 1 min at 30°C, and measured at 510 nm (Gumbar et al., 2023).

MDA levels were determined using the thiobarbituric acid reactive substances method. Briefly, 100 µL of serum was placed into a microtube, followed by the addition of 0.5 mL of 20% TCA and 1 mL of 0.67% TBA solution. The mixture was homogenized, heated at 95°C for 10 min, and then cooled. Absorbance was measured using a UV-visible spectrophotometer at 532 nm. MDA levels were calculated using the regression equation obtained from the standard curve (Ayala et al., 2014).

Histopathological examination and scoring

Liver and kidney tissues were fixed, processed by standard paraffin embedding, sectioned, and stained with hematoxylin and eosin (H&E). Histopathological evaluation was performed at 400× magnification. Liver alterations were scored using the Manja Roenigk scoring system on a semi-quantitative 1–4 scale: 1 = normal hepatocytes, 2 = mild degeneration, 3 = moderate degeneration, and 4 = necrosis or severe cellular alteration. For each animal, 20 cells per field of view were evaluated across five fields of view.

Kidney histopathology was evaluated using a semi-quantitative renal scoring rubric based on glomerular and tubular alterations, including glomerular shrinkage, widening of Bowman's space, tubular epithelial alteration, vacuolization, pyknosis, and karyolysis. The scoring scale was interpreted as 1 = normal or minimal alteration, 2 = mild alteration, 3 = moderate alteration, and 4 = severe alteration. Histopathological scoring was not performed under blinded conditions; this was acknowledged as a study limitation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 27. Data are expressed as mean $\pm$ standard deviation (SD). The IC₅₀ values from the xanthine oxidase inhibition assay were calculated from the concentration-response curve and expressed as mean $\pm$ SD from triplicate measurements.

For biochemical parameters measured in the same animals at D0 and D60, data were analyzed using repeated-measures ANOVA with time (D0 and D60) as the within-subject factor and treatment group as the between-subject factor. The time $\times$ group interaction was used to determine whether changes over time differed among groups. Because only two time points were included, sphericity correction was not required. When significant effects were detected, Bonferroni-adjusted pairwise comparisons were performed. Change-from-baseline values (D60 – D0) were also calculated to support interpretation of the interaction and percent change presented in the tables.

Histopathological scores were analyzed using the Kruskal-Wallis test followed by Bonferroni-adjusted pairwise comparisons because the data were semi-quantitative. Differences were considered statistically significant at $p < 0.05$.

RESULTS

In vitro xanthine oxidase (XO) inhibition assay

The optimized xanthine substrate concentration was 1 ppm, producing an absorbance of 1.0181. The XO inhibition assay, performed in triplicate, showed that EES inhibited XO activity with a half-maximal inhibitory concentration of 30.98 ± 0.64 $\mu\text{g/mL}$. This value indicated lower inhibitory activity than allopurinol, which showed a half-maximal inhibitory concentration of 1.24 ± 0.64 $\mu\text{g/mL}$.

The effects of EES on uric acid levels in hyperuricemia model rats

The effects of EES on uric acid levels in hyperuricemia model rats are presented in Table 1.

Repeated-measures ANOVA showed a significant time $\times$ group interaction for serum uric acid [$F(5,18) = 21.984$, $p < 0.001$]. At D60, serum uric acid was higher in the negative control group than in the normal control group, indicating successful establishment of the hyperuricemic model. Serum uric acid values were lower in the allopurinol-treated and EES-treated groups than in the negative control group ($p < 0.05$).

The effects of EES on creatinine levels in hyperuricemia model rats

The effects of EES on creatinine levels in hyperuricemia model rats are presented in Table 2.

Repeated-measures ANOVA showed a significant time $\times$ group interaction for serum creatinine [$F(5,18) = 34.333$, $p < 0.001$]. At D60, creatinine values were higher in the negative control group than in the normal control group and lower in the allopurinol- and EES-treated groups than in the negative control group.

The effects of EES on SGOT and SGPT levels in hyperuricemia model rats

The effects of EES on SGOT and SGPT levels in hyperuricemia model rats are presented in Table 3.

Repeated-measures ANOVA showed significant time $\times$ group interactions for AST/SGOT [$F(5,18) = 22.916$, $p < 0.001$] and ALT/SGPT [$F(5,18) = 9.081$, $p < 0.001$]. At D60, AST/SGOT and ALT/SGPT values were higher in the negative control group than in the normal control group and lower in the allopurinol- and EES-treated groups than in the negative control group.

The effects of EES on MDA levels in hyperuricemia model rats

The effects of EES on MDA levels in hyperuricemia model rats are presented in Table 4.

Repeated-measures ANOVA showed a significant time $\times$ group interaction for MDA [$F(5,18) = 71.594$, $p < 0.001$]. At D60, MDA values were higher in the negative control group than in the normal control group and lower in the allopurinol- and EES-treated groups than in the negative control group.

Histopathological evaluation of liver and kidney tissues

Liver histopathology

The liver histopathological scores are presented in Table 5.

A higher liver histopathological score indicates more severe hepatocellular alteration. As shown in Table 5, the negative control group showed a numerically higher liver histopathological score than the normal

control group. The EES-treated groups showed lower numerical liver histopathological scores than the negative control group; however, not all pairwise comparisons were statistically significant.

Table 1. Effect of EES on serum uric acid levels in hyperuricemic model rats

Group	Uric acid levels (mg/dL) $\pm$ SD		% Change
	D0	D60	
Normal group	3.65 $\pm$ 0.02	3.63 $\pm$ 0.06 [#]	-0.55
Hyperuricemia model (60% fructose and potassium oxonate) without treatment (negative control group)	3.42 $\pm$ 0.06	6.95 $\pm$ 0.01 ^{*a}	103.22
Allopurinol group	3.24 $\pm$ 0.05	3.32 $\pm$ 0.02 [#]	2.47
EES 100 mg/kg BW	3.05 $\pm$ 0.05	3.28 $\pm$ 0.14 [#]	7.54
EES 200 mg/kg BW	3.18 $\pm$ 0.21	3.26 $\pm$ 0.19 [#]	2.52
EES 400 mg/kg BW	2.59 $\pm$ 0.10	2.64 $\pm$ 0.09 [#]	1.93

Data are expressed as mean $\pm$ SD (n = 4). D0 and D60 biochemical values were analyzed using repeated-measures ANOVA with time as the within-subject factor and treatment group as the between-subject factor, followed by Bonferroni-adjusted pairwise comparisons when appropriate. Symbols in the D60 column indicate pairwise comparisons: *p<0.05 vs. normal control; #p<0.05 vs. negative control; ap<0.05 vs. allopurinol-treated group. EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

Table 2. Effect of EES on serum creatinine levels in hyperuricemic model rats

Group	Creatinine levels (mg/dL) $\pm$ SD		% Change
	D0	D60	
Normal group	0.56 $\pm$ 0.03	0.45 $\pm$ 0.03 [#]	-22.00
Negative control group	0.53 $\pm$ 0.06	0.79 $\pm$ 0.04 ^{*a}	49.06
Allopurinol group	0.52 $\pm$ 0.04	0.37 $\pm$ 0.05 [#]	-28.85
EES 100 mg/kg BW	0.56 $\pm$ 0.05	0.53 $\pm$ 0.07 [#]	-5.36
EES 200 mg/kg BW	0.58 $\pm$ 0.02	0.34 $\pm$ 0.02 [#]	-41.38
EES 400 mg/kg BW	0.52 $\pm$ 0.03	0.27 $\pm$ 0.01 [#]	-48.08

Data are expressed as mean $\pm$ SD (n = 4). D0 and D60 biochemical values were analyzed using repeated-measures ANOVA with time as the within-subject factor and treatment group as the between-subject factor, followed by Bonferroni-adjusted pairwise comparisons when appropriate. Symbols in the D60 column indicate pairwise comparisons: *p<0.05 vs. normal control; #p<0.05 vs. negative control; ap<0.05 vs. allopurinol-treated group. EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

Table 3. Effect of EES on serum AST/SGOT and ALT/SGPT levels in hyperuricemic model rats

Group	AST/SGOT levels (U/L) $\pm$ SD			% Change	ALT/SGPT levels (U/L) $\pm$ SD			% Change
	D0	D60			D0	D60		
Normal group	115.93 $\pm$ 3.79	126.25 $\pm$ 3.53 [#]	8.90		37.13 $\pm$ 2.14	39.15 $\pm$ 2.23 [#]	5.44	
Negative control group	120.90 $\pm$ 1.50	162.68 $\pm$ 6.18 ^{*a}	34.56		34.13 $\pm$ 10.68	64.73 $\pm$ 9.86 ^{*a}	89.66	
Allopurinol group	121.20 $\pm$ 0.68	128.58 $\pm$ 2.91 [#]	6.09		35.88 $\pm$ 3.06	39.30 $\pm$ 3.73 [#]	9.53	
EES 100 mg/kg BW	120.80 $\pm$ 2.55	126.08 $\pm$ 2.70 [#]	4.37		38.03 $\pm$ 4.57	39.83 $\pm$ 4.15 [#]	4.73	
EES 200 mg/kg BW	120.85 $\pm$ 4.30	123.05 $\pm$ 4.27 [#]	1.82		37.03 $\pm$ 4.71	38.08 $\pm$ 3.59 [#]	2.84	
EES 400 mg/kg BW	120.93 $\pm$ 5.49	123.48 $\pm$ 2.39 [#]	2.11		34.00 $\pm$ 2.28	39.25 $\pm$ 3.02 [#]	15.44	

Data are expressed as mean $\pm$ SD (n = 4). D0 and D60 biochemical values were analyzed using repeated-measures ANOVA with time as the within-subject factor and treatment group as the between-subject factor, followed by Bonferroni-adjusted pairwise comparisons when appropriate. Symbols in the D60 column indicate pairwise comparisons: *p<0.05 vs. normal control; #p<0.05 vs. negative control; ap<0.05 vs. allopurinol-treated group. EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

Table 4. Effect of EES on serum MDA levels in hyperuricemic model rats

Group	MDA level (nmol/mL)		% Change
	D0	D60	
Normal group	5.61 ± 0.48	5.18 ± 1.21 [#]	-7.66
Negative control group	5.39 ± 0.37	14.72 ± 0.71 ^{*a}	173.10
Allopurinol group	5.32 ± 1.57	7.06 ± 0.32 [#]	32.71
EES 100 mg/kg BW	5.76 ± 1.52	7.96 ± 0.32 ^{*#}	38.19
EES 200 mg/kg BW	5.25 ± 0.50	8.33 ± 0.50 ^{*#}	58.67
EES 400 mg/kg BW	4.80 ± 0.97	6.71 ± 0.74 [#]	39.79

Data are expressed as mean ± SD (n = 4). D0 and D60 biochemical values were analyzed using repeated-measures ANOVA with time as the within-subject factor and treatment group as the between-subject factor, followed by Bonferroni-adjusted pairwise comparisons when appropriate. Symbols in the D60 column indicate pairwise comparisons: ^{*}p<0.05 vs. normal control; [#]p<0.05 vs. negative control; ^ap<0.05 vs. allopurinol-treated group. EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

Table 5. Effect of EES on liver histopathological scores in hyperuricemic model rats

Group	Liver histopathological score ± SD
Normal group	1.14 ± 0.09 ^a
Negative control group	1.48 ± 0.13 ^{ab}
Allopurinol group	1.66 ± 0.27 ^b
EES 100 mg/kg BW	1.27 ± 0.13 ^{ab}
EES 200 mg/kg BW	1.41 ± 0.14 ^{ab}
EES 400 mg/kg BW	1.14 ± 0.09 ^a

Data are expressed as mean ± SD (n = 4). Differences among groups were analyzed using the Kruskal–Wallis test followed by Bonferroni-adjusted pairwise comparisons. Values with different superscript letters in the same column indicate significant differences (p<0.05). EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

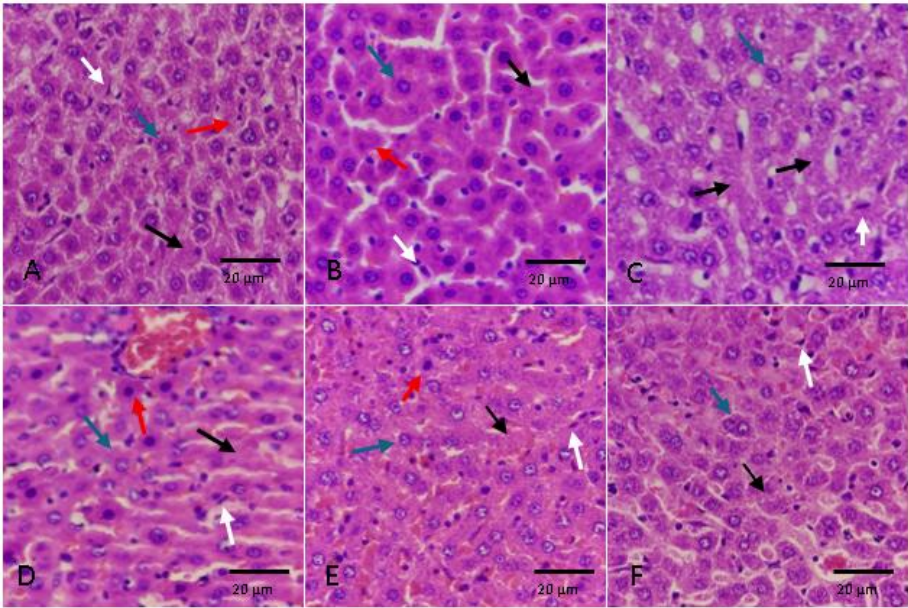


Figure 1. Representative liver histology. (A) normal; (B) negative control; (C) allopurinol; (D–F) EES 100, 200, and 400 mg/kg BW. Arrows: hepatocytes (blue), pyknosis (red), karyolysis (black), Kupffer cells (white). H&E, 400×; scale bar = 20 µm.

Representative liver histopathological images of each experimental group at 400× magnification with hematoxylin and eosin staining are shown in Fig. 1.

Fig. 1 shows representative liver histology. The normal control group showed relatively preserved hepatic architecture, whereas the negative control group showed more evident alterations. EES-treated groups generally showed less prominent tissue alterations than the negative control group.

The liver histopathological images were generally consistent with the numerical scores, but the limited statistical separation among groups indicates that the histological findings should be interpreted cautiously.

Kidney histopathology

The kidney histopathological scores are presented in Table 6.

A higher kidney histopathological score indicates more severe renal tissue alteration. As shown in Table 6, the negative control group showed the highest kidney histopathological score, whereas lower numerical

scores were observed in the EES-treated groups. The clearest statistical separation was observed between the negative control group and the EES 100 mg/kg BW group, while other pairwise comparisons should be interpreted cautiously.

Representative kidney histopathological images of each experimental group at 400× magnification, stained with hematoxylin and eosin, are shown in Fig. 2.

Fig. 2 shows representative kidney histology. The normal control group showed relatively preserved renal architecture, whereas the negative control group showed more evident glomerular and tubular alterations.

EES-treated groups generally showed less prominent kidney tissue alterations than the negative control group, consistent with the lower numerical histopathological scores in Table 6. Because statistical separation was limited, these findings should be interpreted cautiously.

Table 6. Effect of EES on kidney histopathological scores in hyperuricemic model rats

Group	Kidney histopathological score $\pm$ SD
Normal group	1.30 $\pm$ 0.11 ^{ab}
Negative control group	1.60 $\pm$ 0.15 ^b
Allopurinol group	1.36 $\pm$ 0.08 ^{ab}
EES 100 mg/kg BW	1.12 $\pm$ 0.07 ^a
EES 200 mg/kg BW	1.35 $\pm$ 0.07 ^{ab}
EES 400 mg/kg BW	1.27 $\pm$ 0.13 ^{ab}

Data are expressed as mean $\pm$ SD (n = 4). Differences among groups were analyzed using the Kruskal–Wallis test followed by Bonferroni-adjusted pairwise comparisons. Values with different superscript letters in the same column indicate significant differences (p<0.05). EES: ethanol extract of *Erythrina subumbrans*; BW: body weight.

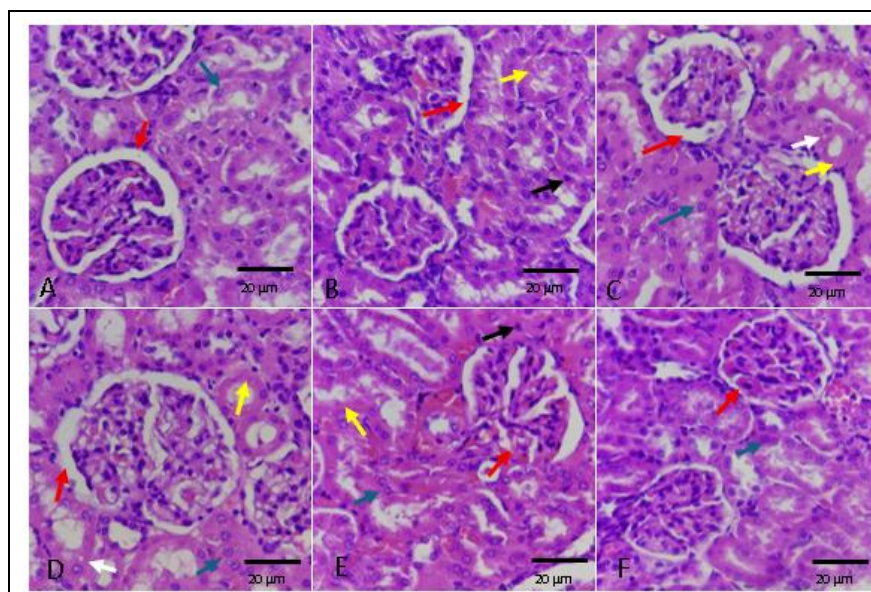


Figure 2. Representative kidney histology.

(A) normal; (B) negative control; (C) allopurinol; (D–F) EES 100, 200, and 400 mg/kg BW. Arrows: glomeruli (red), tubules (blue), vacuolization (white), pyknosis (black), karyolysis (yellow). H&E, 400×; scale bar = 20 μ m.

DISCUSSION

In the present study, the EES showed antihyperuricemic activity in a fructose-potassium oxonate-induced hyperuricemic rat model. The marked increase in serum uric acid level in the negative control group at D60 confirmed that the experimental hyperuricemic condition was successfully established. This finding is consistent with previous reports indicating that potassium oxonate induces hyperuricemia in rodents by inhibiting uricase activity, thereby reducing the conversion of uric acid to allantoin and promoting uric acid accumulation (Zhou et al., 2024). In this preventive/co-treatment model, lower serum uric acid values were observed in the EES-treated groups than in the negative control group under the experimental conditions used in this study.

The urate-lowering effect observed in this study may be partly related to the XO inhibitory activity of EES. XO plays a key role in the final steps of purine catabolism by catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid, while also contributing to reactive oxygen species formation (Liu et al., 2021). The *in vitro* assay showed that EES inhibited XO activity with an IC_{50} of 30.98 ± 0.64 $\mu\text{g/mL}$, indicating lower inhibitory activity than allopurinol ($IC_{50} = 1.24 \pm 0.64$ $\mu\text{g/mL}$). Similar findings have been reported for other plant-derived compounds or extracts in potassium oxonate-induced hyperuricemic models, in which reductions in serum uric acid were associated with XO inhibition and modulation of oxidative or inflammatory pathways (Abdulhafiz et al., 2023; An et al., 2023; Suntornsarattoon et al., 2025). However, the mechanism of EES should be interpreted cautiously because hepatic or serum XO activity *in vivo*, urinary uric acid excretion, fractional excretion of urate, and renal urate transporter expression were not evaluated. Therefore, the antihyperuricemic effect observed in this study cannot be attributed solely to XO inhibition.

Preliminary qualitative phytochemical screening indicated the presence of flavonoids, alkaloids, saponins, tannins, and steroids in EES. Previous studies have reported that *Erythrina* species contain flavonoid compounds, and flavonoid-rich extracts have been associated with antioxidant and enzyme-inhibitory activities (Herlina et al., 2025). In addition, a previous study on *E. subumbrans* leaves reported the presence of polyphenols, flavonoids, and quercetin, suggesting that phenolic constituents may contribute to metabolic and antioxidant effects (Susilawati et al., 2024). Nevertheless, because only qualitative screening was performed and the extract was not standardized using quantitative marker compounds or chromatographic fingerprinting, the phytochemical results should be

interpreted as preliminary characterization rather than direct mechanistic evidence.

A higher creatinine value was observed in the negative control group than in the normal control group at D60. Lower creatinine values were observed in the EES-treated groups than in the negative control group. Similar observations have been reported in experimental hyperuricemia models, where plant-derived compounds or extracts reduced serum uric acid and improved renal biochemical parameters (Abdulhafiz et al., 2023; An et al., 2023; Suntornsarattoon et al., 2025). However, creatinine alone is insufficient to establish a definitive nephroprotective mechanism. Additional parameters, such as blood urea nitrogen, creatinine clearance, urinary uric acid, and renal urate transporter expression, are required to clarify whether the observed effect is related to improved renal excretion, reduced urate burden, or other mechanisms.

AST/SGOT and ALT/SGPT values were higher in the negative control group than in the normal control group and lower in the EES-treated groups than in the negative control group. This pattern is consistent with the concept that hyperuricemia and increased XO activity may contribute to oxidative stress, which may affect hepatic tissue and metabolic function (Du et al., 2024; Liu et al., 2021). However, the interpretation of hepatoprotective activity should remain conservative because serum aminotransferases are biochemical indicators and should be interpreted together with histopathological findings and additional liver injury markers.

MDA levels were elevated in the negative control group, indicating increased lipid peroxidation in the hyperuricemic model. Lower MDA values were observed in the EES-treated groups than in the negative control group. This interpretation is consistent with the reported contribution of xanthine oxidase to oxidative stress during purine metabolism and with reports that elevated uric acid may promote oxidative and inflammatory responses under pathological conditions (Du et al., 2024; Liu et al., 2021). However, because only MDA was measured, further evaluation of antioxidant enzymes and inflammatory mediators is needed to confirm the antioxidant mechanism of EES.

Histopathological findings in the liver and kidney supported the biochemical results, although cautious interpretation remained necessary. In the liver, the negative control group exhibited a numerically higher histopathological score compared to the normal control group, indicating more pronounced hepatocellular alterations in the hyperuricemic model. The EES-treated groups demonstrated lower numerical liver histopathological scores than the negative control

group, with the EES 400 mg/kg BW group showing the lowest score. These observations were generally corroborated by the representative liver histological images, which depicted less prominent tissue alterations in the EES-treated groups relative to the negative control group. However, as indicated by the superscript letters in Table 5, not all pairwise comparisons achieved statistical significance. Furthermore, the allopurinol-treated group exhibited a relatively higher liver histopathological score in the current dataset. Consequently, the liver histopathological findings should be interpreted with caution and should not be used to assert the superiority of any treatment group without further validation.

Histopathological analysis of the kidneys showed that lower numerical kidney histopathological scores were observed in the EES-treated groups than in the negative control group. As indicated by the superscript letters in Table 6, the most distinct statistical differentiation was observed between the negative control group and the EES 100 mg/kg BW group, while other pairwise comparisons should be interpreted with caution. The representative kidney images generally supported the scoring results. However, because histopathological scoring is semi-quantitative, statistical separation was limited, and scoring was not performed under blinded conditions; these findings should be interpreted cautiously.

Repeated-measures analysis showed significant differences in D0-D60 changes among groups for serum uric acid, creatinine, AST/SGOT, ALT/SGPT, and MDA. The overall pattern of results indicated lower hyperuricemia-associated biochemical values in the EES-treated groups within this preventive/co-treatment model. Decreases in serum uric acid, creatinine, AST/SGOT, ALT/SGPT, and MDA levels were observed in the EES-treated groups, along with directionally favorable liver and kidney histopathological scores. Nevertheless, the dose-response relationship was not entirely linear across all parameters. Although EES at 400 mg/kg BW showed a low serum uric acid level and favorable MDA and liver histopathological scores in this dataset, conclusions regarding dose-related safety cannot be drawn without a dedicated toxicity study. Further safety investigations, including subacute toxicity testing, organ index assessment, hematological and biochemical safety evaluations, and blinded histopathological examination, are necessary to confirm the renal and hepatic safety profile of EES.

This study has several limitations. First, the sample size was limited, was determined based on a preliminary experimental design rather than a formal power-based calculation, and may have reduced statistical power and increased variability, particularly for semi-quantitative histopathological interpretation. Second,

the experimental design focused on preventive or co-treatment exposure rather than treatment of established hyperuricemia. Third, the urate-lowering mechanism was not comprehensively investigated because *in vivo* XO activity, urinary uric acid excretion, fractional excretion of urate, and renal urate transporter expression were not assessed. Fourth, the extract was not standardized using quantitative marker compounds or chromatographic fingerprinting, and qualitative phytochemical screening was used only as preliminary characterization. Fifth, histopathological scoring was not performed under blinded conditions, which may introduce observer bias. Sixth, D0 survival orbital sinus/plexus blood sampling was performed under CO₂ anesthesia at <30% of the chamber volume per minute for less than 1 min, as described in the institutional ethics review documents. This route was selected to obtain sufficient serum volume for multiple biochemical analyses from the same animals and to avoid repeated blood sampling. Although this procedure was included in the institutional ethics review process, topical ophthalmic anesthetic or ocular lubricant was not applied. Therefore, the absence of topical ocular anesthesia/lubrication remains an animal-procedure limitation. Finally, oxidative stress assessment was limited to MDA, without evaluation of antioxidant enzymes and inflammatory mediators. Future research should incorporate extract standardization, larger sample sizes based on formal power calculations, blinded histopathological scoring, urinary urate handling, renal transporter analysis, *in vivo* XO activity, subacute toxicity evaluation, and less contentious blood sampling approaches or additional ocular anesthesia/lubrication when orbital sampling is scientifically required.

CONCLUSION

The ethanol extract of *Erythrina subumbrans* leaves showed antihyperuricemic activity in this fructose-potassium oxonate preventive/co-treatment rat model and was associated with improved biochemical parameters. Histopathological findings were directionally favorable but statistically limited. Further work is required to clarify the mechanism, standardize the extract, and define safety.

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.

ACKNOWLEDGMENTS

This research is funded by the Ministry of Higher Education, Science, and Technology, the Directorate General of Research and Development of the Republic of Indonesia, Decree Number 0419/C3/DT.05.00/2025, and Agreement/Contract Number 125/C3/DT.05.00/PL/2025, 7941/LL4/PG/2025. 002/PEN.DRTPM/UBK-DRPM/VI/2025.

GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

During the preparation and revision of this manuscript, the authors used Paperpal AI and ChatGPT (OpenAI) to improve the language, grammar, readability, and organization of the text. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools.

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Contribution	Susilawati E	Azriq AN	Kartikasari	Kaniawati M	Sulaeman A	Levita J
Concepts or ideas	x	x		x		x
Design	x	x		x	x	x
Definition of intellectual content	x	x		x		x
Literature search	x			x		x
Experimental studies	x	x	x			
Data acquisition	x				x	
Data analysis	x		x		x	
Statistical analysis	x		x			
Manuscript preparation	x		x	x		x
Manuscript editing	x	x		x		x
Manuscript review	x	x	x	x	x	x

Citation Format: Susilawati E, Azriq AN, Kartikasari, Kaniawati M, Sulaeman A, Levita J (2026) Antihyperuricemic effect of ethanol extract of *Erythrina subumbrans* (Hassk.) Merr. leaves in a fructose–potassium oxonate-induced male Wistar rat model. J Pharm Pharmacogn Res 14(3): 2715. https://doi.org/10.56499/jppres_14.3.2715

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