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Evaluating the Anti-Hyperuricemic Activity of the Ethanol Extract of *Leucas Lavandulaefolia* in Wistar Rats

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ABSTRACT

Leucas lavandulaefolia, commonly called Lenglengan, is widely used in traditional medicine, and has been reported to possess various pharmacological activities, including hepatoprotective, antipyretic, and anti-inflammatory effects. This study aimed to investigate the anti-hyperuricemic effect of the ethanol extract of *L. lavandulaefolia* leaves. Thirty-five (35) Wistar rats were divided into seven groups of five rats each. Group I: normal control, Group II: negative control (CMC-Na 10 mL/kg BW), Group III: positive control (allopurinol 9.0 mg/kg BW), and groups IV-VII: were administered ethanol extract of *L. lavandulaefolia* leaves at doses of 100, 200, 400, and 800 mg/kg BW, respectively. Prior to the treatments, hyperuricemia was induced in the rats except the normal control by the administration of purine-rich diet comprising chicken liver juice (25 mL/kg twice daily for 14 days), and *Gnetum gnemon* fruit (2 g/kg daily for 14 days). Hyperuricemic rats were treated with the extract, allopurinol, or untreated (negative control) according to their respective groups. Treatments were given once daily for 14 days. Serum uric acid concentrations were measured at intervals of 5 days beginning from the 15th day until the 30th day post-induction. Results showed that the ethanol leaf extract of *L. lavandulaefolia* exhibited a significant and a dose-dependent anti-hyperuricemic activity, with the 800 mg/kg BW dose showing the highest activity, with a 66.27% reduction in serum uric acid concentration on the 30th day post-induction. The ED_{50} was found to be 322 mg/kg BW. Therefore, *L. lavandulaefolia* has the potential to be developed as a natural agent for the treatment of gout.

Keywords: *In vivo, Leucas lavandulaefolia,* Anti-hyperuricemic, Ethanol extract.

Introduction

Hyperuricemia is a condition characterized by high uric acid levels and is increasingly prevalent in many communities. The cases of hyperuricemia have continued to increase in recent years.[1] Due to dietary and lifestyle changes, individuals are experiencing higher uric acid levels at a younger age. Hyperuricemia is strongly associated with hypertension, insulin resistance, obesity and hypertriglyceridemia, which can lead to serious health complications.[2,3] Anti-hyperuricemic drugs, including allopurinol, benzbromarone, and febuxostat are used to treat gout but can cause resistance as well as side effects in the form of polyarthritis, allergies, and liver disorders.[4] Therefore, there is a continued search for natural medicinal ingredients with anti-hyperuricemic activity. *Leucas Lavanduleafolia* commonly called Lenglengan is a medicinal plant which belongs to the Labiateae family. *L. lavandulaefolia* is used in traditional medicine for the treatment of rheumatism, skin diseases, scorpion stings, snake bites, diabetes, fever, constipation, obstructive jaundice, asthma, dyspepsia, paralysis, and wounds.[5,6] The efficacy of a traditional medicinal plant is related to the bioactive compounds it contains. There is available information on the chemical constituents of *L. lavandulaefolia* as well as its biological activities, including anti-inflammatory, antipyretic, and antidiarrheal activities.[5,7]

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The chloroform extract of *L. lavandulaefolia* has been shown to possess antidiabetic effect,[8] while the methanol extract, which contains flavonoid and phenolic compounds has been reported to have antioxidants and antibacterial activities.[9] Phytochemical investigation of *L. lavanduleafolia* leaves reported the presence of alkaloids, saponins, tannins, phenolics, flavonoids, triterpenoids, steroids and glycosides, acacetin, chrysoeriol, linifoliside, linifoliol, lupeol, taraxerone, and vanillic acid.[7,10] The flavonoid glycosides chrysoeriol-6''(OAc)-4'-*β*-glucoside and Crysoeriol -4'-*O*-α-L-rhamnopyranosyl (1-6)-*β*-D-glucopyranoside has been identified in the ethanol extract of *L. lavandulaefolia* leaves.[5,11] Furthermore, *L. lavandulaefolia* has been reported to be effective as an anti-inflammatory agent, which is related to its ability to relieve pain and eliminate inflammation often associated with diseases such as gout.[12] Therefore, this study aimed to determine the anti-hyperuricemic activity of *L. lavandulaefolia* leaves extract *in vivo* using male albino rats. The results from the study are expected to reveal the anti-hyperuricemic potential of *L. lavandulaefolia*, which can be harnessed as a fundamental scientific tool for developing anti-hyperuricemic drugs.

Materials and Methods

Solvents and reagents

Ethanol 96% was obtained from PT Dira Sonita Indonesia, sodium carboxyl methyl cellulose (Na-CMC) was acquired from Sigma-Aldrich, Japan, allopurinol was obtained from PT Hexpharm Laboratores, Indonesia, and uric acid kit reagent was acquired from Sigma-Aldrich, Japan.

Plant collection and identification

Fresh *L. lavandulaefolia* leaves (1 kg) were collected from the Indralaya, Ogan Ilir district in South Sumatera Province, Indonesia (3. 219454 – 3.219562 ºS, 104. 646515- 104.646516°E) in August 2023. The sample was identified as *Leucas lavandulaefolia* with voucher number 570/K-ID//ANDA/VIII/2023 at the Herbarium unit of Research

Center for Biology, University of Andalas, Padang, Indonesian.

Preparation of plant extract
L. lavandulaefolia leaves were dried and ground into a powder form. The powdered leaves (400 g) were extracted three time by maceration in 96% ethanol (2 L) at room temperature for 3 x 24 hours. The extract was thereafter filtered, and the combined filtrate was concentrated under reduced pressure using a rotary evaporator (Eyela type N-1300V-WB, Japan) at a temperature of 70°C and a speed of 60 rpm until a concentrated extract was obtained.[6] The percentage yield of the crude ethanol extract was calculated based on the weight of the powdered sample.

Animals
Thirty-five (35) male albino rats of the Wistar strain, aged 10 - 12 weeks and weighing 150 - 250 g were obtained from the Animal Laboratory Centre at Palembang, South Sumatra, Indonesia. The rats were kept in well-ventilated cages and were acclimatized to the laboratory environment for seven days under adequate lighting (12 h) and a room temperature of 22°C. During the acclimatization period, the rats were fed with standard rodent feed, and allowed access to drinking water *ad libitum.*

Ethical approval
Ethical approval with reference number 022410133 was obtained from the Ethics Committee of Ahmad Dahlan University Yogyakarta, Indonesia. The animal experiment was conducted at the Pharmacology Laboratory, Department of Pharmacy, University of Sriwijaya, following the guidelines for *in vivo* experiments.

Determination of anti-hyperuricemic activity
The anti-hyperuricemic activity was determined using the method of Chen *et al*. (2017)[1] with slight modifications. The rats were divided into seven groups each comprising five rats. The groups are; Group I: Normal control (normal rats without hyperuricemia induction or treatment), Group II: Negative control (hyperuricemic rats administered CMC-Na 1.0% 10 mL/kg BW), Group III: Positive control (hyperuricemic rats administered allopurinol at a dose of 9 mg/kg BW), Groups IV – VII: Treatment groups (hyperuricemic rats administered ethanol extract of *L. lavandulaefolia* leaves at doses of 100, 200, 400, and 800 mg/kg BW). Prior to treatment, the rats were assessed for the baseline blood uric acid concentration designated as normal uric acid levels (H0). Subsequently, hyperuricemia was induced in the rats except the normal control by the administration of a diet designed to increase blood uric acid levels. This diet included chicken liver juice given at a dose of 25 mL/kg BW twice daily for 14 days, and *Gnetum gnemon* fruit administered at a dose of 2 g/kg BW daily for 14 days. Serum uric acid levels were assessed on the 15th day (H15).[13] The rats with hyperuricemia were then treated with *L. lavandulaefolia* extract or allopurinol, or given CMC-Na according to their respect groups as stated above. The serum uric acid levels of the rats were measured after treatment for 5 (H-20), 10 (H-25) and 15 (H-30) days.

Measurement of uric acid levels
Determination of serum uric acid levels was carried out on days 0, 15, 20, 25, and 30. Blood samples were collected from the retro-orbital vein of the rats using a capillary tube. The blood samples were centrifuged (HETTICH Microliter Centrifuge Micro 200R, Germany) for 15 minutes at a speed of 3000 rpm. The serum was taken, and the uric acid levels were measured using a UV-Vis spectrophotometer (Human Humastar100, Germany). A test tube containing 20 µL of distilled water was labeled as the blank and a second test tube contained 20 µL of standard uric acid. Approximately, 1000 µL of uric acid reagent (phosphate buffer, 2,4,6-tribromo 3-hydroxy benzoic acid, 4-amino antipyrine, peroxidase, uricase) was added to each test tube, then shaken homogeneously and left for 10 minutes at 20-25°C. The uric acid levels were measured in triplicates with three rats per group using a spectrophotometer at a wavelength of 546 nm.[13] The percentage decrease in uric acid concentration was calculated by comparing the decrease in uric acid levels measured from test animals given treatment compared to baseline (Equation 1).

$$\% \text{ Decrease AU} = \frac{AU15 - AUx}{AU15 - AU0} \; x \; 100 \quad \ldots\ldots (1)$$

AU15 = Uric acid level on 15th day,
AUx = Uric acid level on the 20th, 25th and 30th day,
AU0 = Basal uric acid levels of rats.

Statistical analysis
Data were analysed for normality of distribution using the Shapiro-Wilk test and homogeneity test was also carried out. This was conducted through the analysis of variance (ANOVA) test using the SPSS® 25.0 (Statistical Package for Social Science), followed by the Duncan's New Multiple Range Test (DNMRT) at a 0.05 significance level. All measurements were performed in triplicate and data were presented as mean ± standard deviation (SD).

Results and Discussion

The extraction of powdered leaves of *L. lavandulaefolia* produced a percentage extract yield of 17.47%. In general, the inhibition of xanthine oxidase (XO) in biological systems using experimental animal model is often used to investigate the anti-hyperuricemia potential of herbal medicines.[14] The experimental animals used in this study were Wistar rats. The rats were assessed for basal serum uric acid levels, and the values ranged from 1.27 ± 0.12 to 1.90 ± 0.37 mg/dL (H0). Normal uric acid levels in rats ranged from 0.5 to 1.4 mg/dL, with values between 1.7 - 3.0 mg/dL classified as hyperuricemia.[13,15] Based on the range of uric acid levels obtained, all test animals were in the normal range. Chicken liver and *G. gnemon* fruit are food rich in purine (xanthin), which can trigger the formation of uric acid in the presence of the XO enzyme.[16,17] Additionally, calcium oxonate (4.5 mg/kg BW) can be used to trigger the formation of uric acid.[18] On the 15th day post administration of a high purine diet, the uric acid levels in the test animals were measured, and the uric acid levels increased significantly ($P < 0.05$) in all the animals, with percentage increase between 110% to 170% above the baseline. The test animals were in a hyperuricemic state with serum uric acid values ranging from 3.43 ± 0.35 to 4.47 ± 0.56 mg/dL, which were above the normal range. For the normal group, the uric acid levels decreased slightly (19%), but remained within the normal range (Table 1). Subsequently, the hyperuricemic animals were given ethanol extract of *L. lavandulaefolia* leaves for 14 days at doses of 100, 200, 400, and 800 mg/kg BW.

Table 1: Serum uric acid levels in rats before and after administration of a high purine diet

Group	Uric acid level (mg/dL) day-		% Increase
	H-0	H-15[a]	
I: Normal	1.53 ± 0.34	1.23 ± 0.08	-19
II: Negative control (-)	1.27 ± 0.12	3.43 ± 0.35	170
III: Positive control (Allopurinol 9.0 mg/kg BW)	1.54 ± 0.27	4.12 ± 0.38	167
IV: LLE (100 mg/kg BW)	1.68 ± 0.49	3.81 ± 0.19	126
V: LLE (200 mg/kg BW)	1.90 ± 0.37	4.47 ± 0.56	135
VI: LLE (400 mg/kg BW)	1.45 ± 0.36	3.86 ± 0.45	166
VII: LLE (800 mg/kg BW)	1.86 ± 0.21	3.91 ± 0.23	110

Values represent mean ± SD (n = 3); H0: Uric acid levels before induction, H15: Uric acid levels on the 15th day after being given chicken liver and *G. gnemon* fruit. [a]significant difference compared to H-0, ($p < 0.05$). LLE: *Leucas Lavandulaefolia* leaf extract.

A suspension of 1.0% Na CMC was used as the negative control, while allopurinol (9.0 mg/kg BW) was used as the positive control.[19] Serum uric acid levels were measured on the 5th, 10th, and 15th day of treatment, and the results are presented in Table 2. The negative control (untreated group) experienced a continuous and significant increase in uric acid levels during treatment until the 30th day (3.43 ± 0.26 – 3.78 ± 0.30), while the normal group of rats had stable serum uric acid levels, which were within the normal range (1.23 ± 0.08 – 2.03 ± 0.11). This observation indicated that rats in the hyperuricemic state and without treatment remained in the hyperuricemic state. In the positive control group, uric acid levels decreased from the outset of treatment (20th day). Allopurinol is a standard anti-hyperuricemia drug that can be used as a reference for measuring anti-hyperuricemic activity.[20] For the extract-treated groups, all the rats showed a decrease in uric acid levels from the 20th to the 30th day, and the highest decrease was observed at the dose of 800 mg/kg BW (Table 2). The extract at all doses tested resulted in a significant decrease in uric acid levels, but only the 400 and 800 mg/kg BW doses decreased uric acid levels to the normal range (< 3 mg/dL). For the groups treated with 100 and 200 mg/kg BW doses of the extract, serum uric acid levels were still outside the normal range (> 3 mg/dL) until the 30th day.

Table 2: Serum uric acid levels in rats after treatment

Group	Uric acid level (mg/dL)			
	H-15	H- 20	H-25	H-30
I: Normal	1.23 ± 0.08	2.03 ± 0.11	1.25 ± 0.13	1.61 ± 0.30
II: Negative control (-)	3.43 ± 0.26	3.63 ± 0.27	3.71 ± 0.28	3.78 ± 0.30
III: Positive control (Allopurinol 9.0 mg/kg BW)	4.12 ± 0.38	3.27 ± 0.38	2.68 ± 0.49	2.39 ± 0.34
IV: LLE (100 mg/kg BW)	3.81 ± 0.19	4.09 ± 0.20	3.97 ± 0.15	3.85 ± 0.06
V: LLE (200 mg/kg BW)	4.47 ± 0.56	3.77 ± 0.41	3.40 ± 0.51	3.15 ± 0.45
VI: LLE (400 mg/kg BW)	3.86 ± 0.45	3.72 ± 0.20	3.1 ± 0.47	2.39 ± 0.45
VII: LLE (800 mg/kg BW)	3.91 ± 0.23	2.91 ± 0.50	2.78 ± 0.42	2.55 ± 0.34

Values represent mean ± SD (n = 3); H15: Uric acid levels on the 15th day after being given chicken liver and *G. gnemon* fruit, H-20 = after treatment for 5 days, H-25: after treatment for 10 days, H-30: after treatment for 15 days. LLE: *Leucas Lavandulaefolia* leaf extract.

Table 3 presents the percentage reduction in uric acid levels across the various groups. From the results, the untreated negative control group did not show a decrease in uric acid level, rather a significant percentage increase in uric acid levels was observed, whereas in the positive control and extract treatment groups, significant percentage decreases in uric acid concentrations were observed, starting from the 20th day. On the 30th day, all extract treatment groups receiving 100 to 800 mg/kg BW doses of *L. lavandulaefolia* leaf extract showed a decrease in uric acid levels, ranging from 24.30% to 66.27%. The uric acid-lowering activity of 100 mg/kg *L. lavandulaefolia* leaf extract was weaker compared to the 200, 400, and 800 mg/kg doses, signifying a dose-dependent effects. In comparison, the positive control group (allopurinol) exhibited a percentage decrease of 67.0% on the 30th day. A previous report state that a 100 µg/mL dose of allopurinol as a xanthine oxidase inhibitor resulted in a 92.07% reduction in serum uric acid level in rats,[21] which was higher than the value obtained in this study using a dose of 9 mg/kg. BW. Treatment group receiving doses of 800 mg/kg BW of *L. lavandulaefolia* leaf extract showed a substantial decrease in uric acid levels on the 20th, 25th, and 30th days, with average percentage uric acid reduction of 48.77, 55.22, and 66.27%, respectively. The ability of *L. lavandulaefolia* leaf extract at a dose of 800 mg/kg BW to reduce uric acid levels in rats was comparable to that of the positive control (allopurinol), which caused a reduction of uric acid levels at 32.09, 55.90, and 67.00% on the 20th, 25th, and 30th day respectively (Table 3). Statistical analysis showed no significant differences ($p > 0.05$) in the percentage reduction of uric acid between the extract at 400 and 800 mg/kg BW doses and the positive control (allopurinol) on the 30th day. However, at lower doses (100 and 200 mg/kg BW) of the extract, statistically significant difference ($p < 0.05$) in uric acid-lowering effect was observed between the extract and the positive control, with the positive control out-performing the extract at these doses. Allopurinol is an antigout agent that competitively inhibits xanthine oxidase.[22,23] It structurally resembles hypoxanthine, which is a substrate in the formation of uric acid. As shown in Figure 1, the linear regression equation of the plot of percentage decrease in uric acid levels versus the extract concentration was used to calculate the dose of the extract that could reduce 50% of uric acid (ED_{50}), and the ED_{50} was determined to be 322 mg/kg BW. The present study has demonstrated that the crude ethanol extract of *L. lavandulaefolia* leaves has potent anti-hyperuricemic activity, which may be due to the inhibition of xanthine oxidase. *L. lavandulaefolia* has not been previously investigated for anti-hyperuricemic activity, hence, this study represents the first report of the anti-hyperuricemic activity of the plant.

Table 3: Percentage decrease in serum uric acid levels in rats on the 20th, 25th and 30th day

Group	% Decrease Day -		
	20	25	30
I: Normal	-266.00 ± 15.00	- 6.60 ± 2.22	-126.00 ± 6.08
II: Negative control (-)	-9.20 ± 2.11	-12.96 ± 2.25	-16.21 ± 3.17[c]
III: Positive control (Allopurinol 9.0 mg/kg BW)	32.09 ± 2.33	55.90 ± 5.21	67.00 ± 4.20[a]
IV: LLE (100 mg/kg BW)	14.90 ± 2.75	19.33 ± 2.11	24.30 ± 2.18[b]
V: LLE (200 mg/kg BW)	1.87 ± 1.01	19.17 ± 2.22	30.63 ± 4.24[b]
VI: LLE (400 mg/kg BW)	6.13 ± 1.15	30.57 ± 3.49	61.22 ± 4.15[a]
VII: LLE (800 mg/kg BW)	48.77 ± 3.32	55.22 ± 5.17	66.27 ± 7.22[a]

Values represent mean ± SD, (n = 3). Values followed by different superscript letter indicate significant difference between means according to Duncan's New Multiple Range Test (DNMRT) at 5% confidence interval. LLE: *Leucas Lavandulaefolia* leaf extract.

Anti-hyperuricemic activity of plant extracts is often attributed to their flavonoid and phenolic contents. Flavonoids are capable of reducing uric acid by competitively inhibiting the action of XO.[24,25] Several flavonoid compounds such as apigenin, luteolin, kaempferol, chlorogenic acid, naringenin, myricetin, quercetin, fisetin, chrysoeriol, and ampelopsin have been reported to have uric acid-lowering effect.[26-28] In addition, flavonoid compounds like quercetin and kaempferol have been reported to act as XO inhibitors with an inhibitory power similar to allopurinol.[29] Prenylated isoflavones such as 6,8-diprenylorobol and 5,7,3′,4′-tetrahydroxy-2′,5′-di(3-methylbut-2-enyl)isoflavone were

found to show potent inhibitory effect against XO.[16] Besides flavonoids, sesquiterpene lactones, such as lychnopholide, eremantholide C, and goyazensolide have been reported to reduce serum uric acid concentration in Swiss mice at doses of 25 mg/kg and 10 mg/kg, respectively.[30,31] The methanol extract of *L. lavandulaefolia* has been reported to contain flavonoids and phenolic compounds.[9] Catechin, luteolin, acacetin, and chrysoeriol compounds, which are flavonoids of the flavone group as well as quercetin belonging to the flavonol group have been reported from the leaves of *L. lavandulaefolia*.[7,10] The presence of quercetin and luteolin is believed to play a role in the uric acid-lowering effect of this plant. In addition, the identified anti-hyperuricemic activity of *L. lavandulaefolia* extract may be related to its ability to reduce inflammation and relieve pain, and this effect is probably linked to the presence of the flavonoid acacetin and chrysoeriol, which have been reported to possess antioxidant and anti-inflammatory activities.[32] Plants containing antioxidant and anti-inflammatory compounds have the potential to be developed for the treatment of gout, rheumatoid arthritis, cardiovascular, and neurodegenerative diseases.

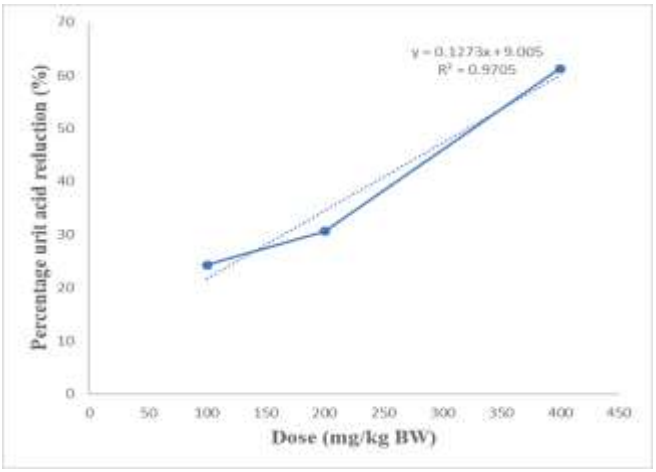

Figure 1: The regression plot between the reduction in uric acid levels and extract doses

Conclusion

The finding from this study have shown that the ethanol extract of *L. lavandulaefolia* leaf possesses potent anti-hyperuricemic activity, which is comparable to that of allopurinol a known xanthine oxidase inhibitor used in the treatment of gout. This observation therefore substantiated the ethnomedicinal use of the plant in the treatment of inflammatory conditions such rheumatoid arthritis. Further studies are needed to define the exact mechanism of the uric acid-lowering effect of *L. lavandulaefolia* leaf extract, and possibly to isolate the bioactive compounds.

Conflict of Interest

The author`s 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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