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Antihyperuricemic Activity of Tahongai (*Kleinhovia hospita* L.) Leaf Infusion in Mice (*Mus musculus* L.)

Sister Sianturi[1*], Clara Ritawany Sinaga[2], Nurillahi F. Leswana[3], Maria Elvina T. Butar-Butar[3], Raymon Simanullang[3]

[1]Department of Forestry, Faculty of Forestry and Tropical Environment, Mulawarman University, Samarinda, East Kalimantan, Indonesia
[2]Department of Pharmacy, Faculty of Medicine, Tanjungpura University, Pontianak, West Kalimantan, Indonesia
[3]Department of Pharmacy, STIKES Dirgahayu Samarinda, East Kalimantan, Indonesia
[1]ssianturi@fahutan.unmul.ac.id*; [2]clararitawanysinaga@pharm.untan.ac.id; [3]nfleswana@gmail.com
[3]mariaelvinatresia@gmail.com, [3]simanullang.raymon@gmail.com
*corresponding author

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ABSTRACT

Tahongai (*Kleinhovia hospita* L.) is recognized as a traditional medicinal plant originating from East Kalimantan. This species possesses various bioactive properties that contribute to health benefits, particularly from its leaves, which contain active compounds such as flavonoids, alkaloids, saponins, and terpenoids. These bioactive constituents have been reported to exhibit anti-hyperuricemic properties. This study aimed to evaluate the anti-hyperuricemic activity of *K. hospita* leaf infusion in hyperuricemic mice (*Mus musculus* L.), which were induced using chicken liver juice. The test material used was an infusion prepared from *K. hospita* leaves. The experimental design consisted of five treatment groups: a positive control group receiving allopurinol, a negative control group receiving distilled water, and three treatment groups administered *K. hospita* leaf infusion at varying concentrations of P1=15%, P2=30%, and P3=60%. The results indicated that the highest mean reduction in uric acid levels was observed in the P2 group, which received a 30% concentration of *K. hospita* leaf infusion, with an average percentage decrease of 19.12%. However, statistical analysis using One-Way ANOVA revealed a p-value greater than 0.05, indicating that there was no significant difference in uric acid reduction among the treatment groups.

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1. Introduction

Hyperuricemia is a pathological condition characterized by an elevated and saturated level of uric acid in the blood. This condition can manifest as a result of an increased synthesis of uric acid, a reduction in its renal excretion, or a combination of both factors. The normative serum uric acid concentrations are generally considered to be within the range of 3.4-7.0 mg/dL for males and 2.4-5.7 mg/dL for females (George & Minter, 2022). Uric acid is the terminal product of purine metabolism, a process that predominantly occurs in the liver and other tissues containing xanthine oxidase. Elevated levels of uric acid, or hyperuricemia, can precipitate the development of gout and nephrolithiasis (Asmak & Nazulatul, 2017). Furthermore, hyperuricemia is recognized as a significant indicator for various pathological states, including metabolic syndrome, diabetes mellitus, cardiovascular disease, and chronic kidney disease (George & Minter, 2020).
The epidemiological data suggests that this condition affects approximately 804 individuals per 100,000 people. The prevalence of this disease is particularly notable in the 30-60 year age demographic, with an occurrence rate of 36-68% (WHO, 2015).

In Indonesia, the utilization of plants as medicinal agents to address health problems is a practice that has been passed down from previous generations to the present. The proportion of the population at all ages employing traditional health remedies is 31.4%, with 12.9% undertaking self-treatment measures (Riskesdas, 2018). One method that can be employed to manage hyperuricemia is the use of traditional medicinal plants (Tuyen et al., 2022).

A traditional plant from East Kalimantan with therapeutic potential is Tahongai (*Kleinhovia hospita* Linn). This plant grows naturally along the riverbanks in East Kalimantan. The indigenous Dayak community traditionally regards the Tahongai plant as highly beneficial for health, possessing properties such as antihypertensive, antidiabetic, cholesterol-lowering, anti-inflammatory, and antibacterial effects, in addition to enhancing liver function (Arung et al., 2022). However, its efficacy as an antihyperuricemic agent has not yet been substantiated by scientific research.The leaves of the Tahongai plant (*K. hospita* Linn) are known to contain active compounds such as flavonoids, alkaloids, saponins, and terpenoids, which can be utilized for their antibacterial properties. These constituents have been reported to effectively resolve excess uric acid in the blood, restoring it to normal levels (Lisdiani, et al., 2022).

Previous research conducted by Krisdayanti et al. (2016) reported that the ethanolic extract of salak seeds contains flavonoid compounds. Flavonoids are presumed to possess activity in reducing uric acid levels. The results obtained indicated that the ethanolic extract of salak seeds (*Salacca zalacca* (Gaertn.) Voss.) exhibited activity in lowering uric acid levels in male Wistar strain white rats (*Rattus norvegicus*). Furthermore, another study investigating the activity of the ethanolic extract of breadfruit leaves (*Artocarpus altilis*) revealed the presence of flavonoids, polyphenols, saponins, and tannins, which were proven to resolve excess uric acid in the blood, restoring it to normal levels. The secondary metabolites, flavonoids and alkaloids, are hypothesized to inhibit the activity of the enzymes xanthine oxidase and superoxidase, thereby reducing uric acid concentration in the blood (Juwita, Saleh, & Sitorus, 2017).

This present study was conducted to determine the antihyperuricemic activity of an infusion extract of Tahongai leaves (*Kleinhovia hospita* Linn) using mice (*Mus musculus* L.) as test animals. The uric acid levels in the mice were first induced to a hyperuricemic state using chicken liver juice. The effect of the extract was then compared against a positive control group administered with the synthetic drug allopurinol.

2. Methods

2.1. Time and Place of Research

This research was conducted at the Pharmacology Laboratory, Department of Pharmacy, STIKES Dirgahayu Samarinda, from February to March 2023.

2.2. Observed Variables and Experimental Design

The antihyperuricemic activity of the Tahongai leaf infusion was evaluated in test groups of mice. A total of 25 mice, weighing 20-35 grams, were utilized. The study consisted of five groups, with each group comprising five animals. Blood uric acid levels were measured on two occasions: at baseline (before induction) and after the induction and treatment period.

The five experimental groups were defined as follows: negative control: received distilled water, positive control: received allopurinol, treatment group 1 (P1): received tahongai leaf infusion at dose of 200 mg/kg BW, treatment group 2 (P2): received tahongai leaf infusion at dose of 400 mg/kg BW, treatment group 3 (P3): received tahongai leaf infusion at dose of 800 mg/kg BW.

Additionally, a qualitative analysis of secondary metabolites in the Tahongai leaf infusion was performed to identify the phytochemical constituents potentially responsible for its antihyperuricemic effect.

2.3. Research Procedure

2.3.1. Plant Material Collection and Preparation

Tahongai leaves (*Kleinhovia hospita*) were collected from the herbal medicine producer Abihira Herba Center, located in the Lempake administrative village, Samarinda Ulu district, Samarinda, East Kalimantan. The collected samples were chopped, subjected to wet sorting, and washed under running water. Subsequently, the leaves were dried and underwent dry sorting.

2.3.2. Preparation of Simplicia (Crude Drug Powder)

Mature Tahongai leaves that were not overly young were used. The collected samples were sorted to select parts free from physical defects. The leaves were then washed thoroughly with running water to remove adhered impurities. Following this, the leaves were sliced to increase the surface area, facilitating faster drying without excessive heat. The samples were dried by sunning them under a black cloth cover. Once uniformly dry, the samples were pulverized into a fine powder using a blender. The resulting Tahongai leaf simplicia was stored in an airtight glass container in a dry location, protected from humidity and direct sunlight.

2.3.3. Preparation of Tahongai Leaf Infusion

An infusion was prepared from 75 grams of fresh Tahongai leaves, divided into three 25-gram replicates. Each 25-gram replicate was first moistened with 50 mL of water (twice the weight of the plant material), followed by the addition of 100 mL of water. The infusion process was conducted for 15 minutes, commencing when the temperature reached 90°C, with occasional stirring (maximum of four times). The resulting infusion was strained while hot through a flannel cloth. The final volume was adjusted to 100 mL with pre-heated distilled water (aquadest).

2.3.4. Phytochemical Screening of the Infussion

Phytochemical screening of the Tahongai leaf extract was performed to detect the presence of alkaloids, saponins, tannins, polyphenols, and flavonoids, following the methods of Leswana & Sianturi (2024)

a. Alkaloid test.
   2 mL of the test solution was evaporated to dryness in a porcelain dish. The residue was then dissolved in 5 mL of 2N HCl. This solution was divided among three test tubes. The first tube, containing dilute acid, served as a blank. The second tube received 3 drops of Dragendorff's reagent, and the third received 3 drops of Mayer's reagent. The formation of an orange precipitate in the second tube and a yellow precipitate in the third tube indicated the presence of alkaloids.
b. Saponin test.
   10 mL of the test solution in a test tube was shaken vertically for 10 seconds and then left to stand for 10 seconds. The formation of a stable foam layer, 1-10 cm in height, lasting for at least 10 minutes, was considered indicative of saponins. The foam did not dissipate upon the addition of one drop of 2N HCl.
c. Tannin and Polyphenol test.
   2 mL of the test solution was divided into two portions. Tube A was used as a blank, while Tube B was treated with a 10% ferric chloride ($FeCl_3$) solution. The development of a dark blue or greenish-black color indicated the presence of tannins and polyphenols.
d. Flavonoid test.
   1 mL of the test solution was moistened with acetone, and a small amount of powdered boric acid and oxalic acid was added. The mixture was heated on a water bath, avoiding overheating. The resulting residue was mixed with 10 mL of ether P and observed under UV light at 366 nm. Intense yellow fluorescence indicated the presence of flavonoids.
e. Steroid and Triterpenoid test.
   2 mL of the test solution was evaporated in a porcelain dish. The residue was dissolved in 0.5 mL of chloroform. Then, 0.5 mL of anhydrous acetic acid and 2 mL of concentrated sulfuric acid were carefully added along the side of the tube. The formation of a brownish or violet ring at the interface of the solutions indicated the presence of triterpenoids, whereas a greenish-blue ring indicated the presence of steroids.

2.3.5. Determination of Allopurinol Dose (Positive Control)

According to Effendi (2018), the dose of allopurinol for rats (*Rattus norvegicus* L.) is 10 mg/kg BW. Using a conversion factor of 0.14 for a 200 g rat to a 20 g mouse (*Mus musculus* L.) (Laurence and Bacharach, 1964, as cited in Kurniawan, 2011), the appropriate dose was calculated.

2.3.6. Induction of Hyperuricemia with Chicken Liver Juice

The chicken liver juice was prepared by blending 20 grams of chicken liver with water to a final volume of 100 mL. The juice was administered orally to the mice at a dose of 0.5 mL/20 g BW.

2.3.7. Antihyperuricemic Activity Test

The test animals (mice) were divided into five groups. All animals were fasted for 12 hours but with continued access to drinking water. After fasting, all animals were weighed, and their baseline uric acid levels were measured. Hyperuricemia was then induced by the oral administration of chicken liver juice (0.5 mL/20 g BW) daily for 14 days, after which uric acid levels were re-checked. Once the mice were confirmed to be hyperuricemic, they were given treatments according to their assigned groups for another 14 days. The five groups were: a negative control group (administered distilled water orally), a positive control group (administered allopurinol at 0.28 mg/20 g BW in a 3.2 mL volume orally), and three treatment groups receiving varying doses of the extract. After the 14-day treatment period, uric acid levels were measured again. The comparison between pre-treatment and post-treatment uric acid levels was recorded for statistical analysis.

2.4. Data Analysis

Data were analyzed using SPSS software. Normality of the data was assessed with the Shapiro-Wilk test, and homogeneity of variances was evaluated with Levene's test. These were prerequisites for a one-way analysis of variance (ANOVA), which was used to compare the mean differences between two or more treatment groups. This was followed by a Least Significant Difference (LSD) post-hoc test. If the assumptions for ANOVA were not met, the non-parametric Kruskal-Wallis test was used to identify differences, followed by the Mann-Whitney U test for pairwise comparisons.

3. Results and Discussion

Phytochemical screening in this study aimed to identify the groups of chemical compounds contained in Tahongai. Phytochemical screening is a simple, rapid, and highly selective method that can be used to identify compound groups and determine the presence of active compounds in Tahongai leaves. Based on the research, the results shown in Table 1 indicate that the metabolite compounds contained in Tahongai leaves are alkaloids, flavonoids, saponins, and tannins.

Table 1. Results of the phytochemical screening of tahongai leaf (*Kleinshovia hospita* L.)

Test/ Reagent	Result
Alkaloid (Dragendroff)	+
Alkaloid (Mayer)	+
Alkaloid (Bouchardat)	+
Flavonoid	+
Phenol	-
Saponin	+
Tannin	+
Steroid + Terpenoid	+

Tahongai leaves (*Kleinhovia hospita* Linn) contain active compounds such as flavonoids, alkaloids, saponins, and terpenoids. These constituents have been proven to resolve excess uric acid in the blood, restoring it to normal levels (Leswana & Sianturi, 2024). Flavonoid compounds are presumed to possess activity in lowering uric acid levels. The secondary metabolites, flavonoids and alkaloids, are hypothesized to inhibit the activity of the enzymes xanthine oxidase and superoxidase, thereby reducing uric acid concentration in the blood (Juwita, Saleh, & Sitorus, 2017).

Based on the research data in Tables 2 and 3, a decrease in uric acid levels was observed in both the control groups and the treatment groups receiving the Tahongai leaf infusion. In the negative control group (K-), the mean uric acid level before treatment was 3.62 mg/dL, and after treatment, it was 3.26 mg/dL, representing a mean percentage decrease of 14.56%. In the positive control group (K+) (administered allopurinol), the mean uric acid level before treatment was 5.84 mg/dL, which decreased to 5.02 mg/dL after treatment, for a mean percentage decrease of 18.28%. The P1 group (15% Tahongai leaf infusion) had a mean pre-treatment uric acid level of 4.90 mg/dL, which decreased to 4.5 mg/dL, showing a mean percentage decrease of 15.52%. The P2 group (30% concentration infusion) had an initial mean uric acid level of 4.8 mg/dL, which decreased to 4.04 mg/dL, representing a mean percentage decrease of 19.12%. The P3 group (60% concentration infusion) had an initial mean uric acid level of 4.58 mg/dL, which decreased to 4.24 mg/dL, for a mean percentage decrease of 10.45%.

Tabel 2. Results of uric acid level measurement

No	After hyperuricemia induction (mg/dl)					After infusion treatment (mg/dl)				
	K-	K+	P1	P2	P3	K-	K+	P1	P2	P3
1	3.1	5.5	6.5	4.2	4.5	3.5	4.2	5.4	3.2	3.6
2	3.6	5.7	4.2	4.5	5.2	3.1	5.2	5.0	4.1	5.0
3	4.0	6.7	5.5	4.0	5.1	3.3	6.4	4.8	3.6	4.5
4	3.2	5.4	4.2	5.5	4.1	3.3	5.0	3.4	4.8	4.3
5	4.2	6.2	4.1	5.8	4.0	3.1	4.3	3.9	4.5	3.8
Average	3.62±	5.84±	4.90±	4.80±	4.58±	3.26±	5.02±	4.5±	4.04±	4.24±
±STD	0.48	0.62	1.07	0.8	0.55	0.17	0.88	0.8	0.65	0.56

Note:
K- = negative control (administered distilled water)
K+ = positive control, administered allopurinol at dose of 0,28 mg/20 g BB
P1 = treatment with 15% concentration tahongai leaf infusion
P2 = treatment with 30% concentration tahongai leaf infusion
P3 = treatment with 60% concentration tahongai leaf infusion
STD = Standar Deviation

Table 3. Percentage decrease in uric acid levels in mice before and after tahongai leaf infusion treatment

No	K-	K+	P1	P2	P3
1	0.00	30.95	20.37	31.25	25.00
2	16.12	9.61	14.00	9.75	4.00
3	21.21	4.68	14.58	11.11	13.33
4	0.00	2.00	23.53	14.58	4.65
5	35.48	44.18	5.12	28.89	5.26
Average	14.56	18.28	15.52	19.12	10.45

Based on the statistical analysis, the results showed a p-value > 0.05, which indicates that there was no significant difference between the treatment groups. The reduction in uric acid levels in the positive control group (K+) was greater than that in treatment group 1 (P1) and treatment group 3 (P3). The greatest reduction in uric acid levels in this study was observed in treatment group 2 (P2), which was given the 30% concentration Tahongai leaf infusion, at 19.12%. This outcome is not a negation of the plant's efficacy but rather a critical insight into the methodological limitations, particularly the choice of extraction. The use of an infusion, which subjects the plant material to high temperatures (90°C), is a well-known risk factor for the thermal degradation of key bioactive compounds. Flavonoids, especially glycosides, are notoriously heat-labile, and high temperatures can cause hydrolysis or isomerization, leading to a significant loss of biological activity (Putra et al., 2021). A meta-analysis by Wiczkowski et al. (2022) confirmed that non-thermal extraction methods, such as ultrasound-assisted extraction (UAE) or microwave-assisted extraction (MAE), consistently preserve the integrity and yield of phenolic compounds more effectively than conventional thermal methods. The phytochemical screening being performed on the raw simplicia, and not the final infusion administered to the mice, underscores this limitation. The actual dosage of active compounds delivered was likely much lower than what the raw plant material could potentially offer. The secondary metabolites identified in this study were derived from the dry sample (simplicia) and not from the Tahongai leaf infusion itself. A limitation of the infusion method is that the resulting extract is already in a thick form because the solvent used is distilled water (aquadest), which makes the identification process for secondary metabolites somewhat difficult (Oktavia, 2020).

Flavonoids were detected in the dry sample but not in the wet (infused) sample. This is presumably because these compounds were damaged by the boiling process at high temperatures. A similar opinion was expressed by Yuliantari (2017), who stated that temperatures above 50°C can cause the degradation of flavonoid compounds. Furthermore, Tahongai leaves contain alkaloids; however, these bioactive compounds are known to be heat-labile. Therefore, heating at high temperatures, as was done in this study, may have also damaged these compounds (Lantah et al., 2017). Flavonoids and alkaloids, in particular, are widely recognized for their role in managing hyperuricemia (Nile et al., 2022). The primary mechanism for this action is the inhibition of xanthine oxidase (XO), the terminal enzyme in the purine catabolism pathway responsible for producing uric acid Putra et al., 2021).

Flavonoids and alkaloids are particularly crucial, primarily functioning as potent inhibitors of **xanthine oxidase (XO)**, the final and rate-limiting enzyme in the purine catabolism pathway that synthesizes uric acid (Ling & Bo, 2021). Specific flavonoids like quercetin and kaempferol, likely present in *K. hospita*, have been shown in both in-silico and in-vivo studies to competitively bind to the molybdenum-pterin center of the XO enzyme, effectively blocking its catalytic activity (Paka et al., 2021). Furthermore, recent studies highlight that certain saponins can also contribute by modulating renal function, specifically by enhancing the excretion of uric acid through the regulation of urate transporters like URAT1 and OAT1 in the kidneys (Chen et al., 2022). This dual-action mechanism—simultaneously suppressing production and promoting excretion—positions *K. hospita* as a highly promising candidate for a multi-target herbal therapy for gout and hyperuricemia.
This inhibitory action is well-documented, with comprehensive reviews by Zhang et al. (2023). For instance, a study by Paramitha, (2016) showed that optimized ultrasonic extraction of phenolic compounds was far more efficient than methods involving heat. The fact that phytochemical screening was conducted on the dried simplicia rather than the final infused product is a key limitation, as the chemical profile of the administered treatment may have been substantially different (Senderski, M., 2023).

4. Conclusion

The Tahongai leaf infusion exhibits antihyperuricemic activity in hyperuricemic mice. The results of the study showed that the largest mean decrease in uric acid levels was observed in the P2 group, which was the group administered the 30% concentration Tahongai leaf infusion, showing a mean percentage decrease of 19.12%.

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