# Effectiveness Test of Bay Leaf Ethanol Extract as Antihyperuricemia Invivo

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***Abstract***

*The imbalance between high production and low excretion of uric acid in the body causes hyperuricemia, which can lead to gout. This disease is the second largest after stroke in Indonesia. Conventional therapy is not free from adverse effects. The tendency of society to go back to nature and the government's "Saintifikasi Jamu" program are efforts to explore safer alternative therapies. One of the plants that has the potential as an antihyperuricemia is bay leaves (Syzygium polyanthum Walp.). The purpose of this study is to optimize the use of scientifically based bay leaves as an antihyperuricemia agent. The research method used is experimental with a pre-posttest design . A total of 20 mice were divided into 5 test groups (induction, comparison, bay leaf extract group (EEDS) with doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW. The effectiveness of antihyperuricemia was tested by inducing mice with 1% chicken liver juice and potassium oxonate. Uric acid levels were measured at T1, T7 and T14 days of the study using a Blood Uric Acid Meter. All groups of test extract doses showed effectiveness as agents to lower uric acid levels significantly compared to the induction group ($p<0.05$). The potential effectiveness of the antihyperuricemia extract showed an effect that was not statistically different from the comparison (allopurinol) ($p>0.05$) at all measurement points. The conclusion of this study shows that bay leaf ethanol extract has the potential as an antihyperuricemia agent, where a dose of 100 mg/kgBW showed the best effectiveness as an antihyperuricemia*

***Keywords: Bay Leaves, Extract, Chicken Liver, Potassium Oxonate, Uric Acid***

## INTRODUCTION

Uric acid is the final product of purine metabolism. Purines are natural substances that form part of the chemical structure of DNA and RNA. Normal uric acid levels range from 3.5–7 mg/dL in men and 2.6–6 mg/dL in women (Kemenkes RI, 2018). When uric acid production increases, or the kidneys fail to eliminate it effectively, blood uric acid levels rise. This condition is called hyperuricemia (Song & March, 2022), defined as uric acid levels above 7.0 mg/dL in men and 6.0 mg/dL in women.

Hyperuricemia can lead to gout, a disease caused by the accumulation of monosodium urate crystals. Gout manifests as painful joint inflammation (gouty arthritis), lumps in certain body parts (tophi), and urinary tract problems such as kidney stones (RJ et al., 2023). Elevated uric acid levels are also linked to the progression of kidney disorders and chronic kidney disease (Shankar et al., 2008).

In recent decades, the incidence of gouty arthritis has increased in both developed and developing countries, particularly among men aged 40–50 years (Singh & Gaffo, 2020). The

prevalence of hyperuricemia varies widely, from 2.6% to 47.2% across populations, while gout prevalence ranges between 1% and 15.3%(Kementerian Kesehatan RI, 2019).

There are two main groups of drugs used to treat hyperuricemia. The first group targets acute inflammation, such as colchicine and indomethacin. The second group works by reducing uric acid levels, including probenecid and allopurinol. In acute attacks, NSAIDs can also be prescribed. However, allopurinol may cause side effects such as allergic reactions, digestive problems, low white blood cell count (leukopenia), joint pain (arthralgia), and itching (pruritus) (Department of Pharmacology and Therapeutics, 2016). Because of these risks, researchers are exploring safer alternative therapies. In Indonesia, there is a growing interest in natural remedies, supported by the government's "Jamu Saintification" program, which promotes preventive research on herbal formulas for hyperglycemia, hypertension, hypercholesterolemia, and hyperuricemia. This program highlights the potential of Indonesia's rich biodiversity for developing plant-based medicines. One promising candidate is bay leaves (Syzygium polyanthum Walp), which have shown potential as an antihyperuricemia agent (Febriyanti et al., 2014).

Previous studies on several plants found that bay leaf water extract at a dose of 200 mg/kg body weight in mice showed the strongest antihyperuricemia effect, reducing uric acid levels by 79.35%, compared to other plants (Darussalam et al., 2019; Hidayah et al., 2018; Ningtiyas et al., 2016; Yanti et al., 2021) . Bay leaves contain flavonoids and tannins, which are believed to play a key role in this effect. These compounds can inhibit the enzymes xanthine oxidase and superoxidase, thereby lowering uric acid levels in the blood. They also block the activity of the cyclooxygenase enzyme, which contributes to anti-inflammatory effects(Hidayah et al., 2018; Hidayat et al., 2021; Muammar, 2014; Nadhifah et al., 2021; Nur et al., 2020; Somalinggi et al., 2023). Based on this evidence, a study was conducted to test the effectiveness of ethanol extract of bay leaves as an antihyperuricemia agent, using 1% chicken liver juice and potassium oxonate to induce high uric acid levels.

## METHODS

This study used an experimental pre-posttest design. In total, 20 mice were divided into five groups: one induction group, one comparison group, and three groups that received bay leaf extract (EEDS) at different doses; 100 mg/kg body weight, 200 mg/kg, and 400 mg/kg

To carry out the experiment, researchers used various tools such as a maceration device, rotary evaporator, water bath, syringes (1 ml and 5 ml), oral sonde, animal and analytical scales, cages, cotton, measuring cups, pipettes, mortars, pestles, spatulas, and a Blood Uric Acid Meter

with uric acid strips. The materials included bay leaves, CMC Na, allopurinol, distilled water, 96% ethanol, flannel cloth, filter paper, potassium oxonate, chicken liver juice, and healthy male mice (20–30 g, aged 2–3 months).

For the extract preparation, 2 kg of fresh bay leaves were washed, drained, dried, and ground into powder. This powdered material (simplicia) was soaked in 70% ethanol (maceration). The extract was then filtered, concentrated with a rotary evaporator, and further evaporated in a water bath until a constant weight was achieved.

The bay leaf sample was verified at the Medanese Herbarium, University of North Sumatra (USU). The extract was then characterized by testing its water content, ash content, ethanol-soluble and water-soluble extract content, and specific gravity. Finally, phytochemical screening was performed to identify compounds such as alkaloids, saponins, quinones, tannins, flavonoids, and steroids/triterpenoids, along with TLC (Thin Layer Chromatography) testing.

The test for antihyperuricemic activity was carried out using a modified method. Each group contained five mice. The groups were Normal group (no treatment); Comparator group (given allopurinol at 10mg/kg body weight); Induction group (given 0.2% chicken liver juice and potassium oxonate at 250 mg/kg body weight, injected intraperitoneally); Extract groups (given bay leaf extract at doses of 100, 200, and 400 mg/kg bodyweight).

To create hyperuricemia, the mice were given 0.2% chicken liver juice daily for 14 days, along with potassium oxonate (250 mg/kg BW, injected) one hour before the test extract was administered. Blood uric acid levels were measured on day 1, day 7, and day 14.

At the start (t0), baseline measurements were taken. Then, the mice received chicken liver juice and potassium oxonate. After one hour, the comparator drug (allopurinol), the carrier solution, or the bay leaf extract was given. Blood uric acid levels were checked again at 60 minutes and 120 minutes after treatment.

Measurements were done using the Easy Touch® device, which reads uric acid levels from a test strip in about 10 seconds. The data were analyzed in two ways Univariate analysis: calculating the mean and standard deviation of uric acid levels for each group, presented in tables and graphs; Bivariate analysis: using ANOVA followed by the Tukey post hoc test, with a confidence level of 95%.

## RESULT

Uric acid levels were measured on days 1, 7, and 14. At each time point, blood samples were taken three times: T0 (before treatment), T1 (after 1 hour), and T2 (after 2 hours).

The choice of these time points was based on earlier studies, which showed that the optimal time to collect blood is 1 hour after induction with potassium oxonate (Ariyanti et al., 2007) . If blood is collected later, uric acid levels tend to drop. This happens because potassium oxonate has a short half-life and is quickly eliminated from the body. Once it is gone, it can no longer block the enzyme uricase, which normally breaks down uric acid into allantoin (Ariyanti et al., 2007) . Therefore, in this study, uric acid measurements were observed up to 2 hours after induction to capture the changes effectively.

**Table 1. Uric acid levels on day 1 of the study (T1)**

| Test Group | Uric Acid Level (T1) | | |
|---|---|---|---|
| | T0 | T1 | T2 |
| Induction | 3.73 ± 0.41 | 5.03 ± 1.49 | 7.15 ± 0.74 |
| Comparator | 7.50 ± 2.84 | 4.45 ± 0.70 | 4.30 ± 0.67 |
| EEDS 400 mg/kg BW | 5.35 ± 0.82 | 4.58 ± 1.06 | 3.65 ± 1.30 |
| EEDS 200 mg/kg BW | 9.30 ± 4.22 | 8.43 ± 3.78 | 5.00 ± 1.02 |
| EEDS 100 mg/kg BW | 6.73 ± 2.65 | 5.35 ± 1.65 | 4.60 ± 1.58 |

**Table 2. Uric acid levels on the 7th day of the study (T7)**

| Test Group | Uric Acid Levels (T7) | | |
|---|---|---|---|
| | T0 | T1 | T2 |
| Induction | 7.08 ± 4.20 | 8.40 ± 4.20 | 10.05 ± 3.45 |
| Comparator | 6.58 ± 2.40 | 3.98 ± 0.71 | 3.35 ± 0.41 |
| EEDS 400 mg/kg BW | 9.05 ± 2.92 | 7.73 ± 2.85 | 5.63 ± 2.20 |
| EEDS 200 mg/kg BW | 5.03 ± 1.29 | 4.98 ± 0.62 | 4.25 ± 0.74 |
| EEDS 100 mg/kg BW | 11.25 ± 6.72 | 5.63 ± 2.96 | 5.33 ± 2.46 |

**Table 3. Uric acid levels on the 14th day of the study (T14)**

| Test Group | Uric Acid Level (T14) | | |
|---|---|---|---|
| | T0 | T1 | T2 |
| Induction | 9.98 ± 2.10 | 11.58 ± 2.67 | 15.90 ± 1.91 |
| Comparator | 5.15 ± 0.59 | 3.93 ± 0.90 | 3.13 ± 0.15 |
| EEDS 400 mg/kg BW | 7.53 ± 0.90 | 6.08 ± 0.88 | 4.73 ± 1.41 |
| EEDS 200 mg/kg BW | 6.10 ± 1.16 | 5.50 ± 1.28 | 4.50 ± 1.37 |
| EEDS 100 mg/kg BW | 7.13 ± 1.63 | 5.73 ± 0.96 | 4.23 ± 1.04 |

**Noted:*

*T0 = time for measuring uric acid levels 1 hour after administration of potassium oxonate and 1% chicken liver juice*

*T1 = time of measurement of uric acid levels 1 hour after oral administration of the test preparation*

*T2 = time of measurement of uric acid levels 2 hours after oral administration of the test preparation*

From Tables 1, 2, and 3, the results showed that one hour after giving 1% chicken liver juice and 250 mg/kg body weight potassium oxonate, the mice had higher blood uric acid levels compared to their normal (pre-induction) condition. This means the induction method worked: the substances successfully blocked the uricase enzyme, which normally converts uric acid into allantoin. As a result, uric acid levels in the blood increased.

Both the bay leaf extract groups (EEDS) and the comparison group (allopurinol) were effective in lowering uric acid levels in the mice. These findings support earlier studies that suggested bay leaf extract has strong potential as an antihyperuricemia agent (Hidayah et al., 2018) . In this experiment, hyperuricemia was induced by giving the mice 1% chicken liver juice and 250 mg/kg potassium oxonate. Chicken liver was chosen because it contains high levels of purines, which are the building blocks for uric acid. Potassium oxonate, on the other hand, works by blocking the uricase enzyme that normally breaks down uric acid into allantoin. When uricase is inhibited, uric acid accumulates in the blood(Saharuddin et al., 2020).

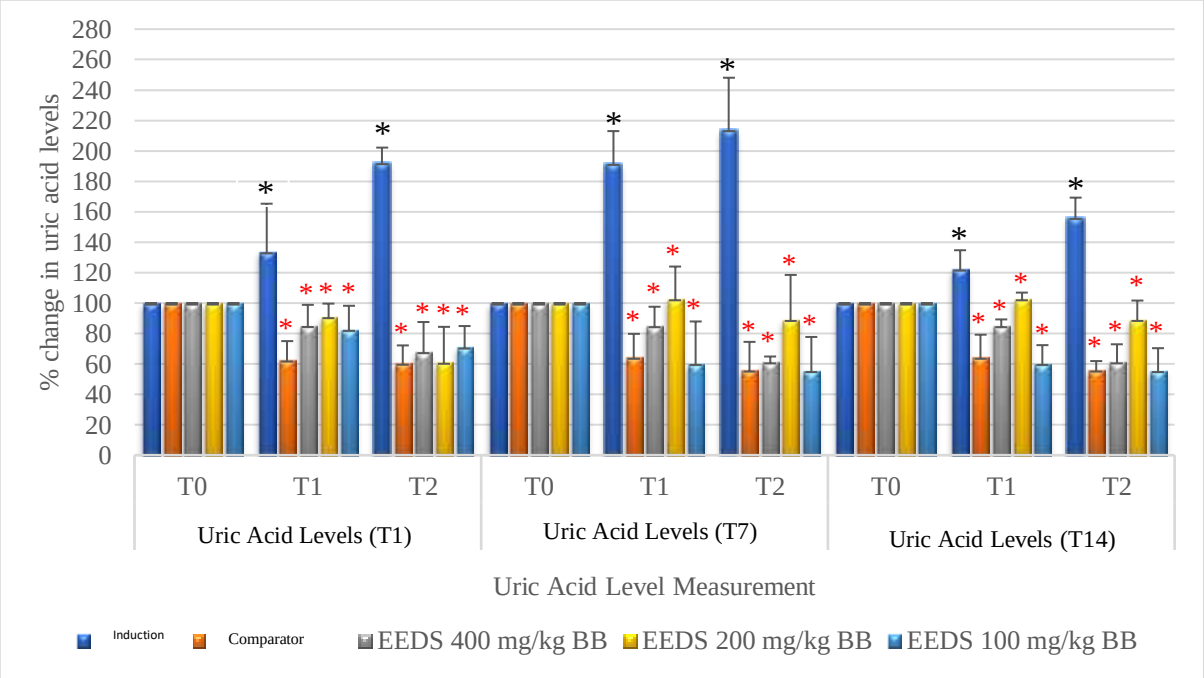


**Figure 1. Graph of percentage changes in blood uric acid levels in test animals**

**Information:*
** = (p<0.05) compared to induction group*
** = (p<0.05) compared to comparison group*

Based on Figure 1, the measurements at T1 (1 hour) and T2 (2 hours) showed that all groups receiving bay leaf extract (EEDS) and the comparison group (allopurinol) had a significant decrease in blood uric acid levels compared to the induction group ($p < 0.05$).

Among the groups, the comparison group (allopurinol) showed the strongest effect in lowering uric acid. However, the difference between allopurinol and the bay leaf extract groups was not statistically significant. This means that bay leaf extract at doses of 100, 200, and 400 mg/kg body weight was able to produce the same antihyperuricemia effect as allopurinol, with a similar onset of action.

These findings are consistent with previous studies, which also reported that bay leaf extract effectively reduced uric acid levels in animal models(Hidayah et al., 2018; Norihsan et al., 2018; Sahensolar et al., 2023).

## DISCUSSION

From Figure 1, the results at T1 (1 hour) and T2 (2 hours) showed that all groups receiving bay leaf extract (EEDS) and the comparison group (allopurinol) experienced a significant drop in blood uric acid levels compared to the induction group ($p < 0.05$).

The comparison group (allopurinol) showed the strongest effect overall. However, the difference between allopurinol and the bay leaf extract groups was not statistically significant. This means that bay leaf extract at doses of 100, 200, and 400 mg/kg body weight was able to produce the same antihyperuricemia effect as allopurinol, with a similar onset of action. These findings are consistent with earlier studies showing that bay leaf extract effectively lowers uric acid levels in animal models(Hidayah et al., 2018; Norihsan & Megantara, 2018; Sahensolar et al., 2023). It is important to note that hyperuricemia is more than just high uric acid it is an independent risk factor for several serious diseases, including gout, chronic kidney disease, hypertension, cardiovascular and cerebrovascular disorders, and diabetes. It is also considered a predictor of premature death. Hyperuricemia occurs when purine metabolism is disrupted, leading to elevated serum uric acid levels.

Although drugs like allopurinol, febuxostat, and benzbromarone are commonly used to lower uric acid, their long-term use can cause significant side effects (Liu et al., 2023). This highlights the importance of exploring safer alternatives, such as plant-based therapies

Allopurinol is a specific inhibitor of the enzyme xanthine oxidase. It works as a substrate analog, meaning it mimics the natural substrate and occupies the enzyme's active site. Because allopurinol is a purine analog, it is metabolized in the liver by xanthine oxidase into its active form, oxypurinol (alloxanthine), which also blocks the enzyme(Suhendi et al., 2011) . As a result, the production of uric acid is reduced, leading to lower uric acid levels in the blood.

Pharmacologically, allopurinol is well absorbed about 80% after oral administration. Like uric acid, it is metabolized by xanthine oxidase, but its metabolite continues to inhibit the enzyme. Because of its long duration of action, allopurinol is usually effective with just one dose per day (Brunton et al., 2008; Department of Pharmacology and Therapeutics, 2016; Pacher et al., 2006) . In this study, the bay leaf extract (EEDS) groups at doses of 100, 200, and 400 mg/kg body weight showed no significant difference in their antihyperuricemic effect.

Normally, increasing a drug dose should increase its response, but after a certain point, the effect plateaus because the maximum response has already been reached.

The active compounds in bay leaf extract believed to lower uric acid are flavonoids. These compounds are reported to inhibit xanthine oxidase, thereby reducing excess uric acid levels. Xanthine oxidase is the enzyme responsible for converting hypoxanthine to xanthine, and then xanthine to uric acid(Hidayah et al., 2018; Umamaheswari et al., 2013).

## CONCLUSION

In conclusion, the ethanol extract of bay leaves has strong potential as an antihyperuricemia agent, showing effects comparable to the standard drug allopurinol. Among the tested doses, the group that received 100 mg/kg body weight of bay leaf extract showed the best effectiveness in lowering blood uric acid levels in the test animals.

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