NASKAH PUBLIKASI

AKTIVITAS ANTIHIPERURISEMIA SECARA IN-VIVO EKSTRAK ETIL ASETAT DAUN KELUBUT (*Passiflora foetida* L.) DARI KOTA SAMARINDA

IN-VIVO ANTIHYPERURICEMIA ACTIVITY OF KELUBUT LEAF ETHYL ACETATE EXTRACT (*PASSIFLORA FOETIDA* L.) *FROM SAMARINDA CITY*

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Aktivitas Antihiperurisemia Secara In-Vivo Ekstrak Etil Asetat Daun Kelubut (*Passiflora Foetida* L.) dari Kota Samarinda

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Abstract

The development of the times creates shifts in lifestyle and eating patterns that trigger hyperuricemia. Hyperuricemia is generally treated with synthetic drugs, but on the other hand, it causes side effects. So the use of natural ingredients such as kelubut leaves can be an alternative treatment. The purpose of this study was to determine the ethyl acetate extract of kelubut leaves has activity as an anti-hyperuricemia. The research uses experimental research methods with a design in the form of a pretest and posttest design. Mice were used and divided into 5 groups, namely the positive control group, the negative control and the group given the extract with three different doses including doses of 250 mg/Kg BW, 125 mg/Kg BW, and 62.5 mg/Kg BW. Mice will be conditioned by hyperuricemia and given different treatments in each group. Data on uric acid levels were analyzed by Kruskal-Wallis and Mann-Whitney. The results of the study showed that administration of the extract at a concentration of 250 mg/Kg BW reduced uric acid levels as much as the positive control group at 120 minutes, but was not statistically different ($p>0.05$) from the positive control. This study concludes that the ethyl acetate extract of kelubut leaves has anti-hyperuricemic activity at a dose of 250 mg/Kg BW showing the best-reducing activity in reducing uric acid levels in mice.

Keywords*: Uric acid; Antihyperuricemic; Kelubut leaves; Passiflora foetida L;* Mice.

Introduction

Along with the development of the times and the entry of globalization, it has created shifts in lifestyle and eating patterns that trigger various health problems, including hyperuricemia.(1) The incidents of hyperuricemia in Indonesia is estimated to be the second largest in joint disease after osteoarthritis.(2) Based on the 2018 Riskesdas, reported from 34 provinces in Indonesia, East Kalimantan ranks 10th with the highest incidence of joint disease with a prevalence of 8,12%.(3)

Hyperuricemia is generally treated with synthetic drugs, but in the long term, it can cause side effects. So the use of natural ingredients such as kelubut leaves can be an alternative treatment. Plants with scientific names *Passiflora foetida* L. can be used to treat cancer, diabetes, stress, blood pressure, anemia, and kidney

disorders, is also antimicrobial and larvicidal.[4] In addition, this plant is traditionally used by residents of the Tanta sub-district, South Kalimantan as a uric acid-lowering drug.[5]

In previous studies, it was reported that the ethyl acetate extract of kelubut leaves. contains metabolites such as alkaloids, steroids, flavonoids, saponins, and tannins.[6] These compounds have been widely reported to have anti-hyperuricemic activity.[7] However, so far not much research has been conducted regarding the activity of kelubut plants, especially as anti-hyperuricemia. Thus this study conducted which aims to determine the ethyl acetate extract of kelubut leaves has activity as an anti-hyperuricemia.

Method

Tools and materials

The tools used in this study included blenders, vacuum rotary evaporators, mortar and pestle, pipettes, easy touch test kits and uric acid strips, filter paper, surgical scissors, measuring flasks, beakers, oral sonde, injection syringes, analytical scales, cages. mice along with places to feed and drink, as well as jars for containers of extract results. The materials used in this study included kelubut leaves, ethyl acetate, distilled water, potassium oxonate, Na CMC, DMSO, allopurinol, melinjo, standard feed, aluminum foil tissue, alcohol swabs, and male white mice which had been declared ethically worthy by the Health Research Ethics Commission State Islamic University of Maulana Malik Ibrahim Malang with ethical clearance No. 04/EC/KEPK-FKIK/40/2023.

Extraction

The kelubut plants obtained from Samarinda city were collected and determined at the Laboratory of the Faculty of Forestry, Mulawarman University. The part used in this study is the leaves. Wet kelubut leaves are sorted wet, washed with running water, then dried, then sorted dry and blended, and sieved to obtain simplicia in powder form. As much as 500 mg of simplicia powder was put into a glass jar and moistened with ethyl acetate solvent in the ratio (1:3) and then stirred until homogeneous. Soaking was carried out for 5 days and repeated maceration 2 times and stirred every 48 hours. The resulting macerate solution is filtered and

concentrated using a rotary evaporator at a speed of 70-110 rpm with a temperature of 40 – 45ºC until a thick extract is obtained.

Preparation of 1% Na CMC Solution

A total of 1 gram of Na CM is sprinkled on the surface of 20 ml of hot water until it swells. Then it is stirred until a thick mass is formed and water is added to make up a volume of 100 ml.[8]

Preparation of extract test stock solution

The ethyl acetate extract of kelubut leaves was made into a stock solution by weighing 25 grams of the extract which was then dissolved in 100 mL of DMSO.

Preparation of Allopurinol Solution

Referring to Masruroh's research (2016), Allopurinol was used at a dose of 10 mg/Kg BW which was made by suspending 24 mg of allopurinol powder into 10 mL of 1% Na CMC.

Preparation of hyperuricemia induction

In treating hyperuricemia, melinjo, and potassium oxonate are used. Melinjo suspension was prepared by dissolving 1 gram of melinjo powder in 3 mL of CMC1% Na, which was then given to mice orally and for potassium oxonate used a dose of 250 mg/kg BW weighing 500 mg and put into a 25 mL volumetric flask, then added 0,9% NaCl solution to the limit mark. The volume of potassium oxonate solution administered to the experimental animals was 0.25 mL/20g BW intraperitoneally.[9, 10]

Antihyperuricemic Activity Test

Mice are first adapted for 7 to 14 days in the laboratory by being given standard food and drink. Then the mice were weighed and marked and the initial uric acid level was measured as the initial level. Then the mice were conditioned to become hyperuricemia by giving potassium oxonate solution intraperitoneally and 1 hour after being given melinjo suspension orally. Then the uric acid levels of the mice were measured after 2 hours of being induced by potassium oxonate. After the mice experienced hyperuricemia which was characterized by uric acid levels reaching >3 mg/dL, then each group was given the following treatment.

1. The positive control group of 3 mice was given allopurinol suspension orally
2. The negative control group of 3 mice was given 1% Na CMC suspension

3. Group A as many as 3 mice were given ethyl acetate extract at a dose of 250 mg/kgBW
4. Group B as many as 3 mice were given ethyl acetate extract at a dose of 125 mg/kgBW
5. Group C as many as 3 mice were given ethyl acetate extract at a dose of 62.5 mg/kgBW

Each group measured uric acid levels within 60 minutes, 90 minutes, and 120 minutes after the treatment was administered by cutting approximately 0.2 cm at the tip of the tail of the mice so that blood came out of the blood which was dripped onto the end of the uric acid strip. In addition, data on uric acid levels is calculated by the percentage of reduction with the following formula.(11)

$$\frac{Average\ levels\ after\ Induction - Average\ levels\ after\ treatment}{Average\ levels\ after\ Induction} \text{ x } 100\%$$

Data analysis

Data on uric acid examination results were analyzed statistically using the Kruskal Wallis test and followed by the Mann-Whitney test on SPSS.

Results and Discussion

The kelubut plant used in this study was obtained from Samarinda city. The determination was carried out at the Laboratory of Ecology and Biodiversity Conversion of Tropical Forests, Mulawarman University. The results of the determination show that the kelubut plant samples are species *Passiflora foetida* L. The part of the plant used for the sample in the research is the leaves. Fresh leaf samples were then processed into simplicia powder. To make it easier to dissolve the compounds in the simplicia, pollination of the samples was carried out by reducing the size of the simplicia particles.(12) The powder used was 500 mg, then soaked in ethyl acetate solvent with a ratio of 1:3 and macerated twice. Ethyl acetate was chosen as the maceration solvent because it is not hygroscopic, has low toxicity, and is semi-polar, attracting both polar and nonpolar molecules.(13)

Maceration was carried out for 5 days in this study. Because the material used is leaves which have a soft consistency and thin cell walls, the maceration process was chosen so that the chemical components can be extracted without heating.(14)

In addition, the maceration method in general can extract most of the metabolites because it does not use heat in the process, so it does not damage the active metabolites contained in kelubut leaves. According to Voight in the research of Pangestu, et al., (2019), maceration is generally carried out within 5 days, after which equilibrium is reached between the material extracted on the inside of the cell and the material extracted on the outside of the cell.[15] Furthermore, re-maceration is needed to increase the removal of compounds that have not previously been attracted by maceration before.[16] Furthermore, the results of the macerate are collected and concentrated with a vacuum rotary evaporator and in a water bath to obtain a thick extract.

The viscous extract obtained in this study was 96.45 grams and the extract yield was 6.43%. Yield is a parameter of extract quality that is calculated by comparing the viscous extract obtained with the simplicia used.[17] In this research, the yield does not meet the <10% requirement. This can be due to various factors, one of which is the polarity of the solvent used. The polarity of the solvent has a strong influence on the extract yield. The stronger the polarity of the solvent, the better the extraction power, and therefore the higher the yield.[18]

In testing the anti-hyperuricemic activity of kelubut leaves, male mice were used as a test animal model. Male mice were chosen because they were considered more stable in providing research data, able to metabolize drugs more quickly, and their body condition was biologically more stable compared to female mice which had hormonal cycles caused by the production of the hormones estrogen and progesterone during the ovulation process. These hormones are released to help remove waste products from the body and produce products that have no physiological function.[19-21]

Mice were adapted for a week before testing, then fasted for 18 hours with only drinking water to ensure that the digestive tract was empty so that drug absorption was not disturbed and uric acid levels did not change.[22] The uric acid levels of the mice were then checked using a uric acid test strip. The initial measurement results presented in table 1 show that in each test group, uric acid levels were <3 mg/dL after fasting. In other words, the mice's uric acid levels were normal after

18 hours of fasting, indicating that the mice used in this study did not experience hyperuricemia before the study.

Table 1. Average Uric Acid Level Examination Results

Group	t0	t1	t60	t90	t120
Positive Control	2,94±0,00	4,43±0,20	4±0,43	3,13±0,15	2,96±0,03
Negative Control	2,94±0,00	5,97±0,55	5,53±0,55	5,23±0,51	4,87±0,47
Group A	2,94±0,00	4,37±0,51	3,25±0,33	2,94±0,00	2,94±0,00
Group B	2,94±0,00	4,2±0,55	3,50±0,50	3,18±0,36	2,94±0,00
Group C	2,94±0,00	4,47±0,51	3,80±0,50	3,45±0,53	3,09±0,26

Information:
t0 : Initial uric acid level
t1 : Uric acid levels after induction
t60 : Acid level at 60 minutes after being treated
t90 : Acid level at 90 minutes after being treated
t120 : Acid level at 120 minutes after being treated

The mice were then conditioned to hyperuricemia by being induced by a high purine diet and a uricase enzyme inhibitor. Melinjo seeds have a high purine content, ranging from 50 to 150 mg/100 grams. According to previous studies, mice that were given melinjo seeds and tested with a spectrophotometer proved to increase blood uric acid levels in male mice up to 81.2% on the 10^{th} day when compared to the normal control group.[9]

Sementara kalium oksonat sebagai penginduksi dengan pemberian secara injeksi intraperitoneal. Potassium oxonate as an inducer by administering an intraperitoneal injection. Various studies have reported potassium oxonate as a component that can increase uric acid levels in animals. In its mechanism, potassium oxonate will inhibit the uricase enzyme so that the conversion of uric acid to allantoin does not occur. Allantoin is a water-soluble molecule that aids in the elimination of uric acid in the urine of rodents. This inhibition has an impact on uric acid which is retained and then accumulates causing it to be unable to be excreted through the urine. The time needed for potassium oxonate to reach peak levels of uric acid in the blood ranges from 1.5 hours to 2 hours.[23] Based on the results of examining uric acid levels in Table 1, it showed that all test groups

experienced hyperuricemia after being given potassium oxonate and melinjo inducers with uric acid levels > 3 mg/dL.[24]

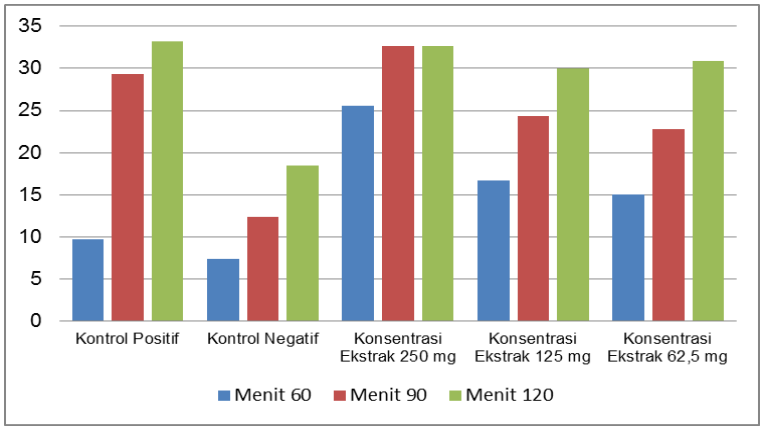

Figure 1. Graph of Decreased Uric Acid Levels at 3 Time Intervals

When the uric acid levels of the mice increased, each group received a different treatment, namely, the positive control group was given allopurinol, the negative control was given 1% Na CMC, and the other three groups received the extract at a dose of 250 mg/KgBW, 125 mg/KgBW, and 62.5 mg/KgBB. The uric acid levels of the mice were then measured at 3 different time intervals. Based on Figure 1, the negative control group experienced a lower decline than the other treatment groups. This is because the negative control group was not given drugs or extracts, only CMC Na which did not have an anti-hyperuricemia effect.[25]

Unlike the case with the group given extracts and drugs, there was a significant decrease. Allopurinol was used as a positive control because it is widely used in the community. Allopurinol is a selective inhibitor and substrate for the enzyme xanthine oxidase, which can permanently inhibit its activity. This drug also functions as an analog substrate (purine) which occupies the active site of the xanthine oxidase enzyme thereby preventing the formation of uric acid.[26] Based on Figure 1, allopurinol decreased at 90 minutes, showing a significant decrease when compared to 60 minutes and 120 minutes. This is because allopurinol has a peak effect at 1.5 hours, which means the drug has experienced a maximum decreasing effect at 90 minutes. This is in line with the research by Kusuma, et al., (2019) that the maximum working effect of the drug allopurinol is 1.5 hours..[27]

Meanwhile, according to Jumain, et al., (2018) Allopurinol has a half-life of 120 minutes, which means that the drug has lost half of its initial level, and the drug's effect begins to decrease.[28]

In the resulting study, the group that was given ethyl acetate extract of kelubut leaves within a period of 60 minutes to 120 minutes showed an effect of reducing uric acid levels, or in other words, ethyl acetate extract of kelubut leaves had an antihyperuricemic effect. In this case, the group given the extract at a dose of 250 mg/KgBW showed the most effective dose in reducing uric acid levels in mice when compared to the group given ethyl acetate extract of kelubut leaves at a dose of 125 mg/KgBW and a dose of 62.5 mg/Kg BW. This is the same with the study of Jumain, et al., (2018) who reported the antihyperuricemic effect of the ethanol extract of African leaves resulting in a decrease in uric acid levels in mice in line with increasing doses of the extract given.[28]

Although the mechanism of ethyl acetate extract of kelubut leaves in reducing uric acid levels is not known for sure. Based on previous studies, the ethyl acetate extract of kelubut leaves contains alkaloids, saponins, tannins and phenolic compounds, and flavonoids.[6] Flavonoids, tannins, and saponins are compounds that have the potential to anti hyperuricemia. Flavonoid compounds work by blocking xanthine oxidase, thereby reducing uric acid levels. Tannins can bind free radicals during the process of converting purines into uric acid; while saponin chemicals function by reducing the activity of the enzyme xanthine oxidase in the blood. Flavonoids, apart from being anti-hyperuricemia, also function as anti-inflammatories by blocking cyclooxygenase and lipoxygenase enzymes, relieving pain associated with hyperuricemia.[29]

Based on the elimination half-life of allopurinol, the data at 120 minutes was used for statistical analysis. Statistical results show that the data is not homogeneous or normally distributed, so the test is usedKruskal-Wallis andMann-Whitney. The Kruskal-Wallis test was used to evaluate the significant differences in uric acid levels in all groups at 120 minutes. The test results obtained $p = 0.034$ (p-value <0,05) which showed that all treatment groups had significantly different uric acid levels at 120 minutes.

To see which groups are different, a test is carried out by Mann-Whitney, The results obtained showed that the average uric acid level between the negative control group and the positive control group and the negative control group with the extract group obtained a Sig value of less than 0.05, which means that there were differences in uric acid levels between the treatment groups. But in the positive control group on the test resultsMann-Whitney when compared to the pk group given the extract had a Sig value greater than 0.05 or uric acid levels were significantly different. This means that kelubut leaves have a very significant effect on lowering uric acid levels when compared to the negative control, but the effect of reducing it is not significantly different from the positive control. This is in line with the study of Wijaya, et al., (2015) who conducted a soursop leaf test which had a very significant effect on lowering uric acid levels when compared to the negative control, but the lowering effect was not significantly different from the positive control.[30]

Based on the research, administration of ethyl acetate extract of kelubut leaves at a dose of 250 mg/Kg BW can reduce uric acid levels as much as the positive control group at 120 minutes compared to giving concentrations of ethyl acetate extract of kelubut leaves at a dose of 125 mg/mL and 62.5 mg/mL, but statistically, these results were not significantly different from the positive control.

Conclusion

The ethyl acetate extract in this study had an effect on reducing uric acid levels in mice with the best dose of 250 mg/kg BW.

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Conflict of interest

There are no potential conflict of interest with the research, authorship, and/or publication of the article, according to all of the authors.

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