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Avocado Seed Ethanol Extract's Ability to Reduce Hyperuricemia in Mice

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Abstract

Background: Hyperuricemia causes uric acid buildup in the blood, often in older people due to how the body processes purines. Studies show avocado seeds *(Persea americana Mill.)* may reduce blood uric acid through their flavonoid content, which fights off oxygen molecules and reduces inflammation, stopping a process called xanthine oxidation. **Objective**: This study aims to assess the effectiveness of avocado seed extract in lowering uric acid levels in male mice. **Method**: Mice were induced with potassium bromate, and the mice were divided into six groups of five individuals each. The groups included a negative control (Na CMC 0.5%), a positive control (allopurinol 10 mg/kg BW), treatment 1 (avocado seed extract 120 mg/kg BW), treatment 2 (avocado seed extract 150 mg/kg BW), treatment 3 (avocado seed extract 180 mg/kg BW), and a normal group (not treated). Checked uric acid levels for seven days. Then, used a statistical test and a BNT test with the LSD method to examine the results. **Results**: The findings showed that avocado seed extract given at a dose of 120-180 mg/kg body weight can reduce uric acid levels in mice. **Conclusion**: The best dose, 150 mg/kg BW, reduced hyperuricemia levels by 37.3%, with a significance value of 0.118.

Keywords: hyperuricemia; avocado seed; mice.

INTRODUCTION

Hyperuricemia is characterized by elevated blood uric acid levels caused by insufficient excretion or excessive production of the acid. Uric acid levels exceeding 7.5 mg/dL in men and 6.5 mg/dL in women are caused by decreased production of uric acid by the kidneys [1]. One of the causes of hyperuricemia is consumption behavior such as consumption of fatty foods, margarine, coconut milk, butter which can affect uric acid excretion [2].

The prevalence of gout worldwide reaches 34.2% [3]. The United States has the most gout sufferers with 8.3 million people suffering from gout. Increased serum uric acid (UA) levels are known to damage silent tissue and increase the risk of various diseases, including metabolic syndrome, type 2 diabetes, obesity, hypertension, dyslipidemia, cardiovascular disease, and chronic kidney disease (CKD) [4].

The main treatment for gout is allopurinol, which inhibits xanthine oxidase and prevents the conversion of hypoxanthine to xanthine and xanthine to uric acid [5]. Long-term use can increase side effects, thus encouraging the search for alternative natural ingredients that are safer and have minimal side effects [2].

There is empirical evidence showing that some medicinal plants can lower uric acid levels in the blood and urine. Recent research extensively uses natural polyphenol compounds, especially flavonoids found in plants or their derivatives. One of them is avocado seed. The flavonoids in the seed act as antibiotics, anti-inflammatories, osteoporosis preventers, vitamin C supporters, and cell structure protectors [6]. The antioxidant activity in avocado seeds also helps inhibit the enzyme xanthine oxidase, which mostly comes from its flavonoid content [7].

A study demonstrated the efficacy of avocado leaf ethanol extract at a concentration of 150 mg/kg body weight per day for 14 days in reducing uric acid levels [8]. Additionally, research by revealed that avocado leaf infusions administered at varying doses resulted in a reduction in uric acid levels of up to 78.85% [9].

These findings suggest that avocado leaves possess significant therapeutic potential, warranting further investigation into the use of avocado seeds. Notably, the high antioxidant content in avocado seeds, which is known to be beneficial to health, is currently underutilized, underscoring the need for further research in this area [10].

This study aims to assess the efficacy of avocado seed *(Persea americana Mill.)* ethanol extract in mitigating hyperuricemia in mice *(Mus musculus L.)*, given the paucity of research on avocado seeds to date.

RESEARCH METHOD

Materials and Equipment

Analytical scales, blender, steam plate, stirring rod, wooden tongs, water bath, mortar, rotary evaporator, filter paper, dropper, alcohol swabs, uric acid meter (EasyTouch GCU®), animal scales, mouse cage, syringe, hot plate, desiccator, pestle and mortar, oven, stopwatch, including test tubes (Pyrex), 50 ml measuring cups (Pyrex), 10 ml measuring flasks (Pyrex), 3L glass jars, spatulas, and syringes, all of which are part of the equipment in this study.

The materials used consisted of 500 g of avocado seeds *(Persea americana Mill.)*, 96% ethanol, 100 mg of allopurinol, sodium carboxymethyl cellulose (Na CMC), potassium bromate ($KBrO_3$), sodium chloride (NaCl), chloroform, hydrochloric acid (HCl), distilled water, magnesium powder, Mayer's reagent, ferric chloride ($FeCl_3$), Lieberman-Burchard reagent, Dragendorff's reagent, uric acid test strips, and four-month-old male mice weighing 20-30 grams.

Research Methods

This study used 30 mice, divided into six groups of five mice each. In this test, all mice were acclimated for a week to ensure that they could adapt. Then, the mice were fasted for five to six hours before induction. Furthermore, the mice were given 1.48 mg of potassium bromate induction per gram of body weight to increase blood uric acid levels, except for group 6 (normal) which was not given induction. The induction of $KBrO_3$ was carried out for 3 days and stopped on days four to seven. After induction, the mice were left for one hour to ensure that the dose of potassium bromate administered caused hyperuricemia. Furthermore, the mice received treatment appropriate for their respective groups every day. Furthermore, blood uric acid levels were assessed 3 hours after treatment and monitored for 7 days [11].

Extraction of avocado seeds *(Persea americana Mill.)*

The sample for this study was an avocado seed *(Persea americana Mill.)* weighing 1.247 g obtained from a fruit juice seller on Jalan Ayahanda, Medan Barat, North Sumatra. The determination test was carried out at the Herbarium Medanense lab at the Faculty of Mathematics and Natural Sciences at the University of North Sumatra, Medan. Next, the seeds were sorted, then dried and blended into a herbal preparation.

After weighing 500 grams of the herbal mixture, it is then soaked in a closed container with 96% ethanol solvent in a ratio of 1:10 for two days, stirring periodically. Furthermore, ethanol is used to remaserate the pulp twice, and the avocado seed extract is filtered. The remaseration result of the extract from avocado seeds is evaporated with a *rotary evaporator* at a temperature of 60. Then a *waterbath* is used to evaporate the extract until a thick extract is produced.

The solvent ethanol 96% was chosen because it is easily obtained, can dissolve polar, semi-polar, and nonpolar compounds, and effectively extract alkaloid and flavonoid compounds that have the potential to be antihyperuricemic agents.

Drying Shrinkage

For drying shrinkage testing, extract is weighed at 1,247 grams, placed in a dish and heated at 105°C for 60 minutes. After that, cool in an exsiccator then place in a desiccator until room temperature. Weigh the dish again until the weight is constant and calculate the percentage of drying shrinkage.

Phytochemical Screening Test

Several phytochemical techniques are used to identify substances. The flavonoid test involves adding magnesium powder and strong hydrochloric acid to 1 milliliter of avocado seed extract; a red, orange, or pink hue is produced when the test is positive. A white or cream-colored precipitate is produced with Mayer's reagent and an orange-red-brown precipitate with Dragendroff's reagent; this is the result of the alkaloid test, which involves heating and filtering the extract after adding HCl and distilled water. To perform the saponin test, the extract is mixed with distilled water, heated, then stirred until a 1-2 cm foam forms, which indicates a positive result. The tannin test shows a green or blue-black color change after the addition of $FeCl_3$. The triterpenoid/steroid test is carried out by dissolving the extract in chloroform, and after the addition of the Lieberman-Burchard reagent, a blue-green color indicates steroids, while a purple-red or brown ring color indicates a positive triterpenoid.

Preparation of 0.5% Na CMC solution

Using volumetric measurements, slowly add half a gram of sodium CMC to one hundred milliliters of distilled water that has been heated to seventy degrees.

Induction production of potassium bromate

The dose of potassium bromate is determined by the dose of potassium in mice, which is 1.48 mg per 20 grams. Measure 148 mg of potassium bromate ($KBrO_3$) and transfer it into a 100 ml measuring cylinder, then fill the cylinder to a total capacity of 100 ml. Induction is done intraperitoneally.

Avocado Seed Extract Suspension Preparation

To make a suspension of 120 mg/kg bw ethanol extract, 120 mg of the extract is weighed, mixed with NaCMC solution and stirred until homogeneous, then poured into a 10 ml volumetric flask. The same procedure is carried out for doses of 150 mg/kg bw and 180 mg/kg bw by weighing the extract according to the dose.

Preparation of Allopurinol suspension

10 tablets of allopurinol 100 mg were taken and crushed in a mortar. After that, 10 mg of allopurinol powder was weighed and dissolved with 100 ml of Na CMC suspension.

Preparation of Test Animals

This study used 30 mice divided into 6 groups, 5 mice each. The study was conducted for 7 days.

Treatment of Test Animals

After the division of the test groups, all mice were fasted for five to six hours and then given potassium bromate induction of 1.48 mg/20 grams of body weight intraperitoneally for 3 days. Except for the normal group, which was not given potassium bromate induction. After one hour, the following treatments were given:
Group 1 (negative control): Mice were given Na CMC suspension.
Group 2 (positive control): Mice were given allopurinol 10 mg/kg.
Group 3 (treatment 1): Mice were given avocado seed extract 120 mg/kg BW.
Group 4 (treatment 2): Mice were given avocado seed extract 150 mg/kg BW.
Group 5 (treatment 3): Mice were given avocado seed extract 180 mg/kg BW.
Group 6 (normal): Mice without treatment.

After 3 hours of treatment, the mice were measured for uric acid levels [11]. The measurement of uric acid levels for 7 days can be seen in **Table 4**.

Blood Uric Acid Level Measurement

After treatment, uric acid levels were measured by puncturing the tail vein of the mouse using a lancet after cleaning it with an alcohol swab. The uric acid strip was attached to the Easytouch GCU® device and the result was displayed after 20 seconds in mg/dL.

Data Analysis

Data analysis was performed using SPSS, starting with an examination of normal blood uric acid levels with the *Kolmogorov-Smirnov* Test. Then the groups were compared using a one-way ANOVA test to see if there were significant differences. If there were, the LSD method of the BNT test was used to see how the groups that received 120 mg/kg BW, 150 mg/kg BW, and 180 mg/kg BW of avocado seed ethanol extract fared.

RESULT AND DISCUSSION

Determination Result

Table 1. Avocado seed determination *(Persea americana Mill)*

Kingdom	Plantae
Divisi	Spermatophyta
Kelas	Dicotyledoneae
Ordo	Laurales
Famili	Lauraceae
Genus	Persea
Spesies	*Persea americana Mill.*

The results of the determination in **Table 1** show that the plant used in this study is Avocado Seed *(Persea americana Mill).*

Extraction Results

Table 2. Yield results

Sample	Avocado seed *(Persea americana Mill)*
Weight of Simplisia (gr)	500 gr
Weight of Extract (gr)	42,1 gr
Yield (%)	8,42%
Drying Shrinkage (%)	18,44%

The yield of avocado seed extract in **Table 2** was obtained at 8.42%. However, the drying shrinkage test result of 18.44% according to [3] does not meet good requirements (<10%), possibly influenced by factors such as temperature, humidity, and moisture content of the material during drying.

Phytochemical results of Avocado seeds

Table 3. Phytochemical

Group of Compounds	Screening Results
Alkaloid	+
Flavonoid	+
Saponin	+
Tannin	+
Triterpenoid	+
Steroid	-

The results of phytochemical identification in **Table 3** show that avocado seeds contain alkaloids, flavonoids, saponins, tannins, and triterpenoids.

Hyperuricemia activity in mice

Hyperuricemia was tested in adult male mice *(Mus musculus L.)*, aged 2-3 months and weighing 20-30 grams, as this age reflects optimal metabolic function. Male mice were chosen to avoid the influence of female hormones on uric acid levels. These animals are used because they are easy to keep, breed quickly, and have human-like morphology [12], [13].

In this study, potassium bromate (KBrO3) 1.48 mg was used as an inducer of hyperuricemia for three days, before being stopped on days 4 and 7. Purine metabolism increased, xanthine oxidase activity increased, and kidney damage occurred due to KBrO3 which interfered with the excretion of uric acid and increased its level [14], [7]. According to [15], mice with uric acid levels between 1.7-3.0 mg/dL experience hyperuricemia.

The average group of mice shows levels above this limit. So, the induction only lasts for three days. The negative control (-) used in this study was sodium carboxymethyl cellulose with a concentration of 0.5%. This group only received 0.5% sodium carboxymethyl cellulose and 1.48 mg potassium bromate, without allopurinol and avocado seed extract. Na-CMC does not substantially reduce uric acid levels due to the absence of a pharmacological effect [14].

Allopurinol functions as a positive control in this study. Allopurinol, the main treatment for gout, inhibits the formation of uric acid and is administered orally after the rapid decrease produced by potassium bromate [2]. The comparison group in this study is the Normal group, which does not receive induction therapy or extracts. This study used avocado seed extract at different doses: K3 (120 mg/kg), K4 (150 mg/kg), and K3 (180 mg/kg).

Effectiveness Test Results of Avocado Seed Extract (Persea americana Mill.) in Reducing Hyperuricemia in Mice (Mus musculus L.)

Table 4. Average reduction of uric acid

Treatment group	Uric Acid Level in Mice Blood							Average decrease	Percentage (%)
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
K1	4.4±1.7	4.2±1.6	3.3±1.5	4.0±1.7	3.9±1.7	3.7±1.8	3.7±2.0	3,88	11,7%
K2	2.7±2.5	2.3±2.0	1.7±0.2	1.4±0.2	1.3±0.2	1.2±0.2	1.2±0.3	2,05	62,5%
K3	3.8±1.3	3.7±1.3	3.6±1.3	3.5±1.3	3.4±1.3	3.3±1.2	3.3±1.5	3,51	16.7%
K4	3.9±0.6	2.8±0.6	2.7±0.6	2.6±0.6	2.5±0.6	2.4±0.6	2.4±0.6	2,75	37,3%
K5	3.9±1.0	3.8±1.0	3.6±1.0	3.5±1.0	3.2±1.1	3.2±1.1	3.1±1.2	3,48	21%
K6	1.0±0.3	0.9±0.1	1.2±0.1	1.0±0.2	1.1±0.3	1.1±0.2	1.1±0.3	1,05	-

Description:
K1 (group 1): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given a suspension of Na CMC.
K2 (group 2): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given a suspension of allopurinol at a dose of 10 mg/kg.
K3 (group 3): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given avocado seed extract *(Persea americana Mill.)* 120 mg/kg of body weight
K4 (group 4): Test animals were induced with potassium bromate 1.48 mg/20 grams BW and given avocado seed extract *(Persea americana Mill.)* 150 mg/kg BW
K5 (group 5): Test animals induced with potassium bromate 1.48 mg/20 grams BW and given avocado seed extract *(Persea americana Mill.)* 180 mg/kg BW
K6 (group 6): Normal test animals.

Table 4 shows the results of the seven-day assessment of uric acid levels in mouse blood. In the sixth group, which was the control group, the average blood uric acid level was 1.05 mg / dL. The normal range of uric acid in mice is between 0.5 - 1.4 mg / dL [15]. Research found that in Groups 1 and 5, the average level of uric acid with potassium bromate induction in mice was 3.3 mg / dL after three days of testing.

Hyperuricemia occurs in mice when uric acid levels are between 1.7 and 3.0 mg / dL. The average uric acid level in mouse blood decreased by 2.05 mg / dL after 7 days of allopurinol treatment ***Table 4***, with a 62.5% decrease in the K+ group **Table 4**.

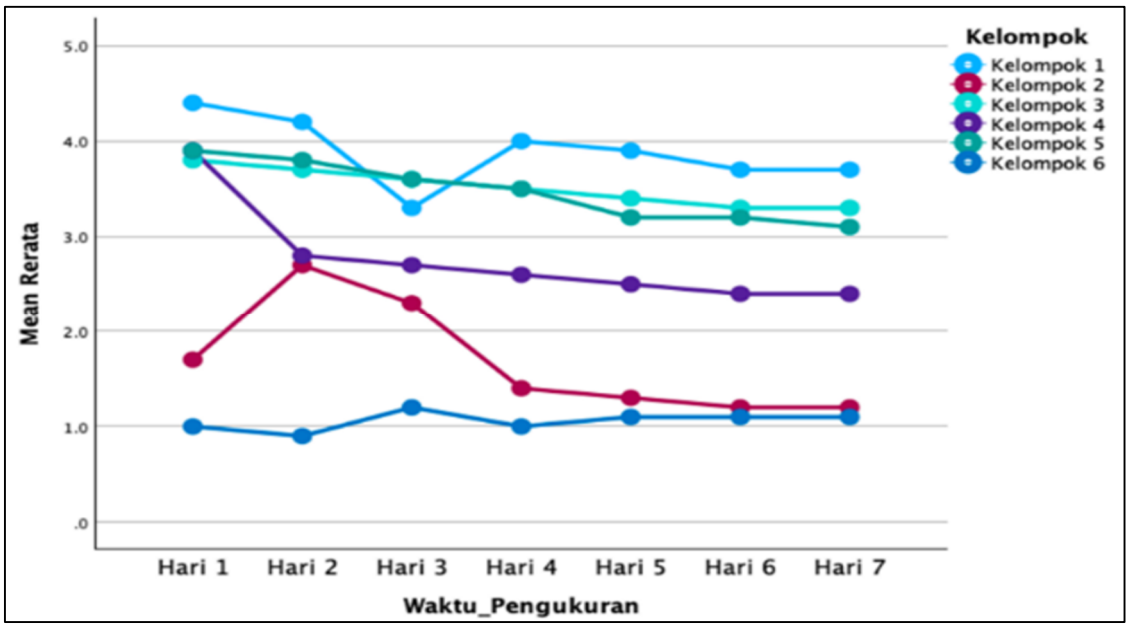

Figure 1. Average Reduction of Urate in Mice

Description:
K1 (group 1): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given a suspension of Na CMC.
K2 (group 2): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given a suspension of allopurinol at a dose of 10 mg/kg.
K3 (group 3): Test animals were induced with potassium bromate 1.48 mg/20 grams of body weight and given avocado seed extract *(Persea americana Mill.)* 120 mg/kg of body weight
K4 (group 4): Test animals were induced with potassium bromate 1.48 mg/20 grams BW and given avocado seed extract *(Persea americana Mill.)* 150 mg/kg BW
K5 (group 5): Test animals induced with potassium bromate 1.48 mg/20 grams BW and given avocado seed extract *(Persea americana Mill.)* 180 mg/kg BW
K6 (group 6): Normal test animals

The research findings shown in **Figure 1** indicate that group K2 (allopurinol) and group K4 (avocado extract 150 mg/kgBB) experienced the most substantial reduction in uric acid levels, with K2 showing the most rapid and consistent reduction. The control group (K6) had the lowest values due to the absence of induction or therapy. The high dose (K5) effectively reduced uric acid levels; however, excessive antioxidant activity may cause oxidative stress and reduce efficacy [17]. The low dose (K3) showed a modest reduction though less effect compared to the larger dose, while the negative control (K1) showed no appreciable change.

The most prominent decrease in uric acid levels occurred in groups K2 and K4, which showed excellent results until the seventh day. Unlike group K6, the test animals were not given potassium bromate at a dose of 1.48 mg per 20 g body weight or given avocado seed extract *(Persea americana Mill.)* at doses of 120 mg/kg, 150 mg/kg, and 180 mg/kg body weight. The drug had good results in reducing uric acid levels in most groups.

Post-experiment, blood uric acid levels were assessed using statistical analysis using the normality test (one sample Kolmogorov-Smirnov). The results of the normality test showed normal distribution ($p > 0.05$), allowing continuation of the one-way ANOVA test. If $p \leq 0.05$ in the one-way ANOVA test, then the least original difference test (BNT) should be performed using the LSD technique.

The data was found to be normally distributed, as all groups had p values greater than 0.05 in the Kolmogorov-Smirnov normality test. When looking for evidence of group differences or homogeneity, one-way ANOVA is the way to go. A significant value of 0.338 ($\geq$ 0.05) was shown by the homogeneity test, indicating that all test animal data were homogeneous. Since the data met the conditions, the ANOVA test was run.

Furthermore, a p value of less than 0.05 was obtained from the results of the treatment group comparison test using one-way ANOVA on uric acid measurement data. Using the least significant difference test (BNT) with LSD, the findings showed that over a 7-day period, blood uric acid levels varied in all animal groups. After administration of doses of 120, 150, and 180 mg/kg bw, respectively, the LSD test showed statistically significant differences between the positive and negative controls.

One alternative theory is that the effect of KBrO3 as an inducer in antihyperuricemia trials is similar in all groups of mice. According to Vogel et al. (2008) cited in [14], KBrO3 negatively affects the kidneys, causing increased uric acid levels and impaired uric acid clearance.

After seven days of taking ethanol extract from avocado seeds and receiving potassium bromate induction therapy, blood samples were taken to determine the results. Mice with high blood uric acid levels can benefit from oral administration of K3, K4, and K5 ethanol extracts from avocado seeds after treatment for 1-7 days.

In this study, it was found that the uric acid level of this group was lower (120 mg/kg BW, K3 group) compared to the larger doses of avocado seed extract (K4 and K5). Reduction in uric acid levels and blocking of xanthine oxidase enzyme is not possible with moderate doses of flavonoids [11]. When compared to the reduction seen at moderate and high doses, the 16.7% reduction in uric acid at low levels was much smaller. The reduction in cholesterol levels was shown to be 18.1% lower at 125 mg/kg of avocado seed extract, and 31.2% lower at 250 mg/kg [16]. Avocado seeds contain flavonoids, which have antioxidant effects and can prevent LDL plaque formation in blood vessels by enhancing the antioxidant characteristics of cells [16].

With an average decrease of 21% and a significance value of 0.107, testing avocado seed extract at high doses (180 mg/kg bw, K5) effectively reduced uric acid levels. Although there is an increase in the activity of metabolite components, the effectiveness of the extract may be reduced due to oxidative stress and other imbalances caused by higher concentrations [17].

The presence of antioxidant phytochemicals such as flavonoids and tannins which are also high in polyphenols are responsible for this. Compared to the doses administered in Groups 3 and 5, the findings showed that the medium dose of avocado seed extract (150 mg/kg bw, K4) was more efficient in reducing uric acid levels in mice. This chemical has significant antioxidant characteristics and suppresses the formation of xanthine oxidase, making it more efficient than allopurinol in reducing uric acid levels [18], [10].

CONCLUSION

The results showed that among the three groups tested, group K4, consisting of 150 mg/kg body weight of avocado seed extract, significantly reduced uric acid levels in mice more effectively than groups K3 and K5. Avocado seeds have high concentrations of polyphenolic antioxidants called flavonoids and tannins, which contribute to their effectiveness. [18] and [10] found that this drug effectively lowers uric acid levels after allopurinol because it inhibits xanthine oxidase production and has considerable antioxidant ability. To find out how avocado seed extract *(Persea americana Mill.)* affects uric acid production, researchers need to test different doses and keep the mice in the laboratory for a longer period of time.

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