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Antihyperuricemia of Lemongrass Extract (*Cymbopogon citratus*) on Male Mice with Potassium Oxonate and Chicken Liver Juice Induced

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ABSTRACT

Background: Hyperuricemia is a pathological condition characterized by increased blood uric acid levels exceeding 7 mg/dL. The use of medicinal plants for managing hyperuricemia has garnered significant attention.
Aims & Methods: This study aims to evaluate the anti-hyperuricemic effect of lemongrass extract (*Cymbopogon citratus*) in a hyperuricemia model using 18 Deutsche Denken Yoken (DDY) mice induced with potassium oxonate and chicken liver juice. Lemongrass simplicia was extracted by maceration using 96% ethanol. Test animals were induced with hyperuricemia by administering chicken liver juice at a dose of 0.5 mL/20 g body weight (BW) for seven consecutive days and potassium oxonate at a dose of 250 mg/kg BW on the eighth day. The test animals were divided into six test groups, namely group 1 was the normal; group 2 was the negative control; group 3 was the positive control (allopurinol at 13 mg/kg BW); groups 4 – 6 were treatment lemongrass extract at doses of 350, 700, and 910 mg/kg BW, respectively.
Result: The results showed that group 6 mice statistically significantly reduced uric acid levels ($p = 0.001$, $p < 0.05$). *Cymbopogon citratus* extract effectively reduces uric acid levels and holds substantial potential as a uric acid-lowering agent, supporting its empirical use in managing hyperuricemia.

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1. Introduction

Uric acid is a metabolite of purines, which are components of nucleic acids found in the nuclei of body cells. Elevated uric acid levels lead to the deposition of monosodium urate crystals in both articular and non-articular structures. Uric acid manifests as excruciating arthritis (gout flares) triggered by an innate immune response to the deposition of monosodium urate crystals (Dalbeth *et al.,* 2021; Kussoy *et al.,* 2019).

According to the Global Burden of Disease (GBD) database, the global prevalence of gout in 204 countries, analyzed by age, sex, and economic development levels in 2019, revealed 53.9 million prevalent cases and 9.2 million incident cases of gout. These numbers have more than doubled since 1990, with the prevalence and incidence of gout rising faster in men than in women and are projected to continue increasing by 2030 (Han *et al.,* 2024). In New Caledonia, the prevalence of hyperuricemia was 67.0% (threshold 360 µmol/L or 6 mg/dL) and 37.0% (threshold 420 µmol/L or 7 mg/dL) among the multiethnic population aged 18–60 years, comprising Polynesians, Europeans, Melanesians, and other ethnic groups (Bardin *et al.,* 2022). Indonesia ranks fourth in the world for the number of gout sufferers, with 35% of cases occurring in men over 45 years old and a prevalence of 54.8% in the elderly. Based on medical diagnoses, the incidence rate reaches 7.3% (Silpiyani *et al.,* 2023). In the prevalence of non-communicable diseases (NCDs) in Yogyakarta, 42.7% of patients had gout, with women having a higher average rate (Rusmini *et al.,* 2023).

Pharmacological therapy to reduce uric acid levels can be achieved using uricosuric agents, which decrease renal reabsorption, and uricostatic agents, which inhibit xanthine oxidase activity (Fardin & Onsi, 2019). One commonly recommended uric acid-lowering therapy for gout is allopurinol, which inhibits xanthine oxidase. It is generally recommended as the first-line therapy for gout management (Ojha *et al.,* 2017; Stamp & Chapman, 2020). However, the use of allopurinol can cause several side effects, including hepatitis, nephropathy, hypersensitivity, and skin rashes. Therefore, exploring alternative xanthine oxidase inhibitors with minimal side effects is crucial (Dong *et al.,* 2016).

Various studies have demonstrated that lemongrass (*Cymbopogon citratus*) has properties to reduce uric acid and has traditionally been used to treat gout. In Mount Ungaran, Central Java, its stems and leaves are boiled and consumed (Utami *et al.,* 2019). Research conducted at a Palembang community health center found that warm compresses using lemongrass decoction effectively reduce arthritis pain (Dwi, 2023). A study on older women with hyperuricemia showed that incorporating lemongrass into their diet significantly reduced uric acid levels in the intervention group (Maulid *et al.,* 2020). Preclinical studies on lemongrass decoctions demonstrated their effectiveness in lowering uric acid levels in rats (Pelleng *et al.,* 2019; Rachmanda Haris, 2022). Additionally, in vitro, research revealed that lemongrass inhibited xanthine oxidase activity by 44.3%, compared to 83.9% inhibition by allopurinol (Saivarshine *et al.,* 2020).

The objective of this study is to determine the anti-hyperuricemic effect of lemongrass extract (*Cymbopogon citratus*) on male mice (*Mus musculus*) induced with potassium oxonate and chicken liver juice and to identify the optimal dose of lemongrass extract to reduce uric acid levels.

2. Methods

2.1 Tools and Materials

The materials used in this study included NaCMC (Sigma-Aldrich®), potassium oxonate (Sigma-Aldrich®), 0.9% NaCl (Satoria Pharma®), quercetin standard (Sigma-Aldrich®), aluminum chloride (Merck®), allopurinol standard (BPOM RI), ethanol p.a. (Merck®), sodium acetate (Merck®), ether (Merck®), concentrated sulfuric acid (Merck®), uric acid FS TBHBA reagent (ProLiNE®), uric acid standard FS (ProLiNE®), concentrated lemongrass extract (*Cymbopogon citratus*), fresh chicken liver, and distilled water. Plant determination was conducted at Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, under registration

number 302/UN2.F3.11/PDP.02.00/2024. The identified plant was confirmed as lemongrass (*Cymbopogon citratus*) with species code JI24-P-95 *Cymbopogon citratus* (DC.) Stapf from the family Poaceae.

The tools used in this study included a UV-visible spectrophotometer (Shimadzu®), cuvettes (Shimadzu®), centrifuge (Hettich®), centrifuge tubes (Hettich®), moisture analyzer (Petra Mechatronics®), furnace (Thermolyne Thermo Scientific®), vacuum pump (Rocker300®), analytical balance (Ohaus®), micropipettes (Eppendorf®), desiccator (Dianrui®), digital animal scale (SF400®), EDTA tubes (Vaculab®), incubator (Memmert®), oven (Memmert®), syringes (Terumo®), measuring cylinders (Iwaki®), beakers (Pyrex®), Erlenmeyer flasks (Pyrex®), test tubes (Pyrex®), glass rods (Iwaki®), dropper pipettes, oral gavage tubes for mice, mortar, and pestle, Büchner funnel, porcelain crucible, stirring rods, mouse cages, and spatulas.

2.2 Animals

The test animals used in this study were male mice of the Deutschland Denken Yoken (DDY) strain, aged 6–8 weeks, with body weights ranging from 15–25 grams. The animals were obtained from the research and development center of the Indonesian Food and Drug Authority (BPOM RI, 2023). A total of 18 mice were used, divided into six treatment groups, with three mice per group based on the maximum and minimum sample size calculated using One-Way ANOVA (Arifin & Zahiruddin, 2017; Maryana *et al.,* 2024). This study was approved by the Ethics Committee of Universitas Negeri Malang under approval number No.20.06.1/UN32.14.2.8/LT/2024. The rats were maintained properly and according to ethical guidelines (Widiyani & Listyawati, 2022).

2.3 Sample Preparation

The raw material of lemongrass (stalks and leaves) was obtained from BALITTRO, Bogor, and harvested in the morning. After wet sorting and indirect drying, the dried Simplicia was finely ground and sieved (mesh 60). The extraction process was carried out using the maceration method with 96% ethanol for three days with periodic stirring. The filtrate was separated using filter paper and concentrated using a rotary evaporator at a temperature of 40–50 °C to obtain a thick extract (Alfiyanti *et al.,* 2023).

2.4 Alkaloid Screening

A sample of 500 mg was mixed with 1 mL of 2N hydrochloric acid and 9 mL of distilled water, heated over a water bath for 2 minutes, then cooled and filtered. The filtrate was divided into three test tubes, each containing 0.5 mL. Two drops of the following reagents were added to each tube: Mayer's reagent (positive for alkaloids indicated by a white to yellowish precipitate), Bouchardat's reagent (positive indicated by a brick-red precipitate), and Dragendorff's reagent (positive indicated by a brown precipitate) (Sulistiyowati & Kusumaningrum, 2023).

2.5 Flavonoid Screening

A 1 g extract sample was added to 10 mL of hot water, boiled for 5 minutes, and filtered while hot. A 5 mL portion of the filtrate was mixed with 0.1 g magnesium powder, 1 mL concentrated hydrochloric acid, and 2 mL amyl alcohol, then shaken and allowed to separate. The color in the amyl alcohol layer was observed. Flavonoids are reduced with Mg and HCl, resulting in red, yellow, or orange colors (Wahid & Safwan, 2020).

2.6 Tannin Screening

A 5 g sample was extracted with 10 mL distilled water and filtered, and the filtrate was added with 1–2 drops of ferric chloride reagent. The formation of dark blue or greenish-black colors indicated a positive result (Halimu *et al.,* 2020).

2.7 Saponin Screening

A 0.5 g sample was mixed with 10 mL of hot water, cooled, and shaken vigorously for 10 seconds until foam appeared. After standing for 2–5 minutes, foam formation was observed, and one drop of 2N HCl was added. If the foam persisted for more than 30 seconds, it indicated the presence of saponins (Adi *et al.,* 2017).

2.8 Terpenoid Screening

A 100 mg extract was dissolved in 5 mL of ether and evaporated in an evaporating dish. The residue was treated with two drops of acetic anhydride and one drop of concentrated sulfuric acid. Red-green or violet-blue colors indicated a positive result for terpenoids (Sulistyarini *et al.,* 2019).

2.9 Determination of Total Flavonoid Content

A quercetin standard solution was prepared at a concentration of 1000 ppm, and the maximum wavelength (λ max) was determined within the range of 370–450 nm, identifying the highest absorption peak as the maximum wavelength (Syifa *et al.,* 2022). A standard curve was constructed by diluting the 1000 ppm stock solution to 4, 5, 6, 7, and 8 ppm. Aliquots of 0.04 mL, 0.05 mL, 0.06 mL, 0.07 mL, and 0.08 mL were pipetted into 10 mL volumetric flasks, followed by the addition of 3 mL ethanol p.a., 0.2 mL 1M sodium acetate, 0.2 mL 10% AlCl3, and distilled water to the mark. A blank was prepared using all solvents and reagents except the analyte (quercetin). The mixtures were incubated at room temperature for 30 minutes, and absorbance was measured. A calibration curve was plotted, and the linear regression equation was determined (Haresmita & Pradani, 2022).

A 0.25 g sample of thick lemongrass extract was dissolved in distilled water to a final volume of 25 mL. A 1 mL aliquot was transferred into a 10 mL volumetric flask, adding 3 mL ethanol p.a., 0.2 mL 1M sodium acetate, 0.2 mL 10% AlCl3, and distilled water to the mark. Triplicate samples were prepared and incubated at room temperature for 30 minutes, and absorbance was measured. The absorbance values were applied to the linear regression equation $y = ax + b$ obtained from the quercetin calibration curve, where y represents absorbance, and x represents the flavonoid concentration in the extract (Syifa *et al.,* 2022).

2.10 Yield calculation

The thick extract obtained was weighed in a pre-tared dish, and the percentage yield was calculated using the formula: Yield (%) = (Initial Raw Material (g)Thick Extract (g)) × 100% (Dewatisari, 2020).

2.11 Loss of drying calculation

Two grams of extract were placed in a porcelain dish previously dried at 105°C for 30 minutes and tared. The dish containing the thick extract was placed in an oven at 105°C for 3 hours, then cooled in a desiccator under closed conditions. The process was repeated until a constant weight was achieved. The dish containing the dried extract was weighed, and the loss on Drying was calculated using the formula: Loss on Drying (%) = (Weight Before (g)− Weight After (g) / Weight Before (g)) × 100% (Djoko *et al.,* 2020).

2.12 Ash content calculation

Two grams of extract were weighed in a crucible dish, with three replicates prepared. The dishes were previously dried at 105 °C for 30 minutes and tared. The extract was incinerated in a furnace at 600 °C for 7 hours. The resulting ash was allowed to cool in a desiccator for 30 minutes and weighed. Ash content was calculated using the formula: Ash Content (%) = (Ash Weight (g) / Initial Weight (g)) × 100% (Nawafila & Muhimmatul, 2023).

2.13 Moisture content calculation

A 1 g sample was placed in the measuring plate of a moisture analyzer, which was set for moisture content analysis. This step was repeated three times for sample replicates. The analysis time for each sample ranged from 2 to 10 minutes, with the moisture content displayed on the moisture analyzer screen (Rodhiyah *et al.,* 2024).

2.14 Preparation of potassium oxonate induction and chicken liver juice

Potassium oxonate was administered to mice at 250 mg/kg BW. The solution was prepared by weighing 500 mg of potassium oxonate and dissolving it in 0.9% NaCl to a final volume of 25 mL. The solution was administered intraperitoneally at 0.25 mL/20 g BW (Kim *et al.,* 2019; Saharuddin & Titawanno, 2020). Fresh chicken liver juice was prepared every three days by grinding 20 g of fresh chicken liver into a fine consistency and dissolving it in distilled water to a final volume of 100 mL. The juice was stored in a refrigerator at 2 °C – 8 °C and administered orally once daily at 0.5 mL/20 g BW (Widyastiwi *et al.,* 2022).

2.15 Preparation of allopurinol suspension

The typical human dose of allopurinol is 100 mg, which was converted to a dose for mice weighing 20 g using a conversion factor of 0.0026, resulting in a dose of 13 mg/kg body weight (BW). The suspension was prepared by dissolving 100 mg of standard allopurinol in 0.5% Na CMC to a final volume of 50 mL. It was administered orally at 0.13 mL/20 g BW (Sinata *et al.,* 2022).

2.16 Hyperuricemia induction

Chicken liver juice was administered orally once daily for seven consecutive days at a 0.5 mL/20 g BW dose. On the eighth day, potassium oxonate was administered intraperitoneally at 0.25 mL/20 g BW. Two hours after the potassium oxonate induction, the test animals received treatments according to their respective groups (Afiah *et al.,* 2023; Widyastiwi *et al.,* 2022).

2.17 Experimental Design

Eighteen male mice were acclimatized for 7 days. The mice were divided into six groups as follows: Group I: Healthy mice were provided with food and water ad libitum; Group II (Negative Control): Mice induced with potassium oxonate and chicken liver, without lemongrass extract or allopurinol; Group III (Positive Control): Mice induced with potassium oxonate and chicken liver, given allopurinol at a dose of 13 mg/kg body weight (BW); Group IV: Mice induced with potassium oxonate and chicken liver, given lemongrass extract at 350 mg/kg BW dose; Group V: Mice induced with potassium oxonate and chicken liver, given lemongrass extract at a 700 mg/kg BW dose; and Group VI: Mice induced with potassium oxonate and chicken liver, given lemongrass extract at 910 mg/kg BW dose. The solution was prepared by weighing 5 g of extract and dissolving it in distilled water to a final volume of 100 mL. The doses administered orally were 0.14 mL/20 g BW, 0.28 mL/20 g BW, and 0.36 mL/20 g BW (Djahi *et al.,* 2021; Tambunan, 2022). The treatments were administered daily for 14 consecutive days. Uric acid levels were measured one hour after the final dose of the test compounds. Blood samples were collected via euthanasia using the terminal cardiac puncture method (Aduwamai, 2019; Agusfina & Julio, 2022). Uric acid levels were measured using a Uric Acid FS TBHBA-ProLiNE® kit as a reagent for the enzymatic photometric TBHBA (2,4,6-tribromo-3-hydroxybenzoic acid) test method, with Uric Acid FS-ProLiNE® Standard Calibrator at a concentration of 6 mg/dL. Uric acid levels were analyzed using a UV-Vis spectrophotometer (Rahayu *et al.,* 2022; Sulistiyowati & Kusumaningrum, 2023).

2.18 Statistical Analysis

The results of the uric acid level are expressed as mean ± SD. Differences between groups were assessed by one-way ANOVA using Statistical Package for the Social Sciences (SPSS for Windows, version 25.0). Post hoc testing was performed for inter-group comparison using the least significant difference (LSD). The significance level was p-values ≤ 0,05.

3. Results

Plant determination was conducted to verify the authenticity of the materials used in this study. The plant identification was performed at Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, with certificate number 302/UN2.F3.11/PDP.02.00/2024. The simplicia was extracted using the maceration method with 96% ethanol as the solvent. Ethanol was chosen because it effectively dissolves various active compounds in plant materials and can extract non-polar, semi-polar, and polar compounds (Alfiyanti *et al.,* 2023; Wendersteyt *et al.,* 2021). The thick extract obtained from the extraction process weighed 203.5 g.

The organoleptic examination results for the thick extract of *Cymbopogon citratus* showed that the extract was dark brownish-black in color and had a characteristic aromatic odor, a bitter taste, and a thick texture (Tri *et al.,* 2024). Phytochemical screening of the *Cymbopogon citratus* extract revealed the presence of alkaloids, flavonoids, tannins, saponins, and terpenoids (Table 1). These compounds have varying polarities: flavonoids, tannins, alkaloids, and saponins are polar, while terpenoids are non-polar (Ema *et al.,* 2022; Tri *et al.,* 2024).

Table 1. Phytochemical screening test results of Specific Parameter Qualitative Test of Lemongrass (*Cymbopogon citratus*)

Type of test	Results of the Qualitative Test
Alkaloid	+
Flavonoid	+
Tannin	+
Saponin	+
Terpenoid	+

The flavonoid content in *Cymbopogon citratus* extract was determined, with an average result of 4.702 ± 0.246 mg QE/g (Table 2). The total flavonoid content of *Cymbopogon citratus* can be influenced by several factors, including plant genetics, plant age, harvest time, the part of the plant used, and the environmental conditions where the plant grows. These factors may affect the quality of the plant extract (Maria *et al.,* 2020).

Table 2. Flavonoid content results of the specific Parameter Quantitative Test of Lemongrass (*Cymbopogon citratus*)

Sample replication	Results of flavonoid content (mgQE/g)
1	4,605
2	4,982
3	4,519
Average	4,702 ± 0,246

Non-specific characteristics of the simplicia include environmental factors during the extract preparation process (Table 3). The extract of *Cymbopogon citratus* (DC.) Stapf met the requirements for good yield weight > 10% (Badriyah & Farihah, 2022). The drying loss of the extract was 14.07%, indicating the maximum amount of compounds lost during the drying process, including water and other

volatile compounds. The moisture content of *Cymbopogon citratus* extract met the moisture content requirement of <10% (Nawafila & Muhimmatul, 2023). The ash content of *Cymbopogon citratus* extract had an average of 7.276%, and the plant part can influence the mineral content used (Hidayati *et al.*, 2018).

Table 3. Results of Non-Specific Parameter Test of Lemongrass (*Cymbopogon citratus*)

Non-specific parameter testing	Results of the non-specific parameter test
Yield (%)	20,35
Loss on Drying (%)	14,07
Moisture Content (%)	2,144 ± 0,488
Ash Content (%)	7,276 ± 0,236

Hyperuricemia induction using a combination of potassium oxonate and chicken liver juice was carried out, and a preliminary test was conducted to determine if the induction method could increase serum uric acid levels in mice as a model of hyperuricemia. The uric acid levels of the two groups are shown in Figure 1. The mice induced with hyperuricemia had an average uric acid level of 3.8 mg/dl, with values between 1.7-3.0 mg/dl indicating hyperuricemia (Fitrya & Muharni, 2014).

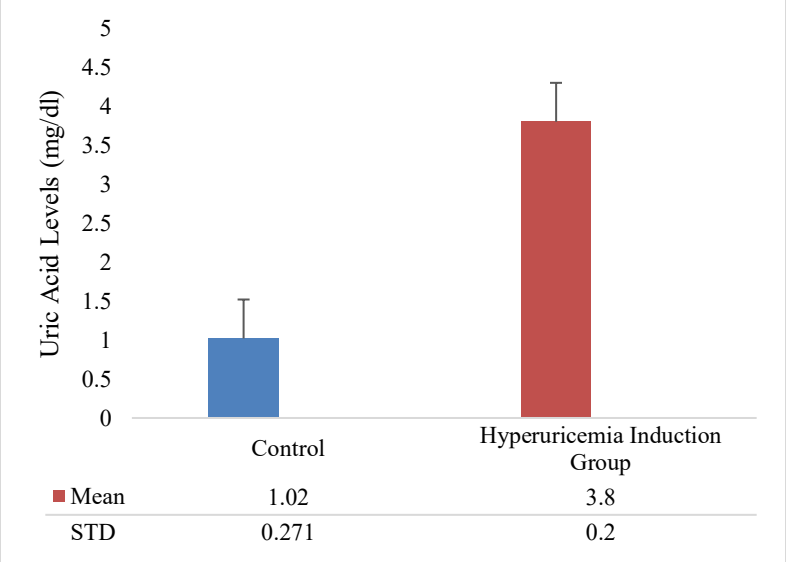

Figure 1. Uric Acid Level Preliminary Induction Test

The induction method was consistent with previous studies that used a combination of chicken liver juice and potassium oxonate as a hyperuricemia induction model (Afiah *et al.*, 2023; Ferani *et al.*, 2014; Nurul *et al.*, 2018; Saharuddin & Titawanno, 2020; Widyastiwi *et al.*, 2022). Chicken liver has a high purine content, and potassium oxonate reduces uric acid excretion and inhibits the enzyme uricase, establishing the hyperuricemia model in rodents (Tang *et al.*, 2017).

The changes in uric acid levels at the end of the 14-day treatment period are shown in Figure 2. Statistical results showed significant differences in uric acid levels between groups based on the ANOVA test ($p = 0.001$).

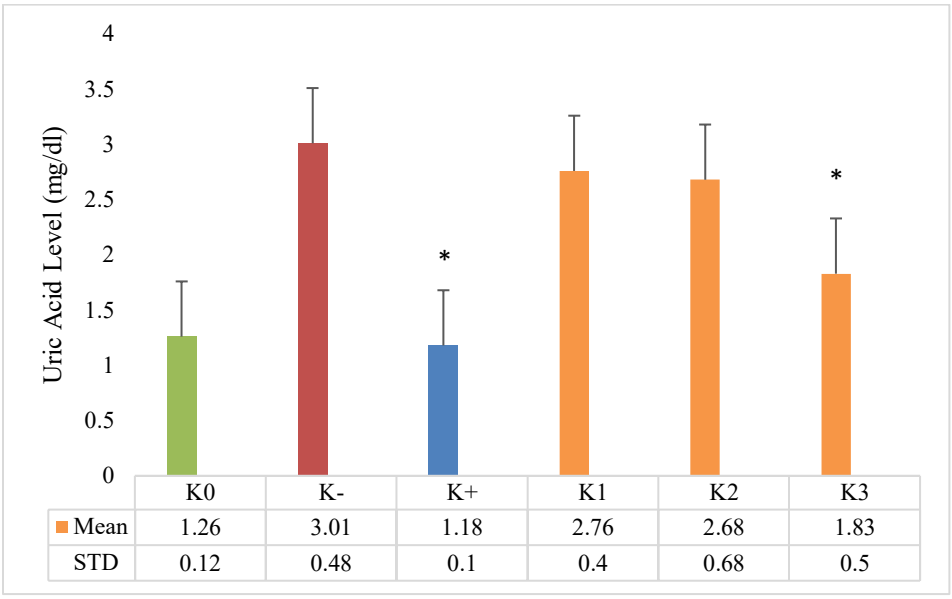

Figure 2. Uric Acid Levels After Treatment. *Significant difference vs. control group at P <0.05. K0 (Normal group), K- (Negative control group), K+ (Positive control group, treated with allopurinol at 13 mg/kg BW), K1 (Mice hyperuricemic treated with *Cymbopogon citratus* extract at 350 mg/kg BW), K2 (Mice hyperuricemic treated with *Cymbopogon citratus* extract at 700 mg/kg BW), K3 (Mice hyperuricemic was treated with *Cymbopogon citratus* extract at 910 mg/kg BW). Post Hoc LSD testing revealed that the negative control group differed significantly from the normal group ($p = 0.000$) and the allopurinol-treated group ($p = 0.000$). However, the negative control group did not differ significantly from those receiving 350 mg/kg BW ($p = 0.473$) and 700 mg/kg BW ($p = 0.372$). Conversely, the group receiving the highest dose of 910 mg/kg BW showed a significant difference compared to the negative control group ($p = 0.006$).

The negative control group, which was only given NaCMC, still experienced hyperuricemia because NaCMC has no therapeutic effect (Simorangkir, 2020). In contrast, the group treated with *Cymbopogon citratus* extract showed reduced uric acid levels, likely due to the extract's properties as a xanthine oxidase inhibitor, the enzyme responsible for uric acid formation. The most significant decrease in uric acid levels was found in the group given the 910 mg/kg BW dose, suggesting that this dose had a more substantial uricosuric and anti-hyperuricemia effect than the other doses.

Cymbopogon citratus extract has inhibited xanthine oxidase activity (Saivarshine *et al.*, 2020). This effect is strengthened by flavonoids, which act as enzyme inhibitors, reducing uric acid production and oxidative stress (Ilkay & Fatma, 2021; Zhang *et al.*, 2018). However, herbal therapies may lead to toxicity with long-term use. Therefore, further evaluation of the extract's toxic effects through toxicity testing is necessary to ensure its safety (Rahman *et al.*, 2019).

5. Conclusions

After a series of discussions and data analyses, it can be concluded that *Cymbopogon citratus* extract contains flavonoids, alkaloids, tannins, saponins, and terpenoids. The total flavonoid content in *Cymbopogon citratus* extract is 4.702 ± 0.246 mgQE/g. The induction of the hyperuricemia model with chicken liver juice and potassium oxonate increased uric acid levels to 3.8 ± 0.2 mg/dl. The administration of *Cymbopogon citratus* extract at a dose of 910 mg/kg BW significantly reduced uric acid levels with a p-value of 0.001 ($p < 0.05$) in male DDY strain mice compared to the 350 mg/kg BW and 700 mg/kg BW doses. This study demonstrates the potential of *Cymbopogon citratus* extract as an anti-hyperuricemia agent.

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