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Research Article

ANTIHYPERURICEMIC ACTIVITY OF ETHANOL EXTRACT OF *SYZYGIUM CUMINI* LEAVES ON POTASSIUM OXONATED-INDUCED RATS

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ABSTRACT

Objective: This study was conducted to investigate the effect of extract of *Syzygium cumini* on serum uric acid levels of rats induced by potassium oxonate.

Methods: A total of 30 male Wistar rats were randomly divided into six groups, consist of one normal group (without treatment) and five groups that were induced by potassium oxonate 250 mg/kg bw intraperitoneally for 7 days. The ethanol extract of *S. cumini* leaves dose (100, 200, and 400 mg/kg bw) was administered orally 1 h after the potassium oxonate exposure during 7 days. On day 8, blood samples were collected for serum uric acid determination.

Result: Ethanol extract of *S. cumini* leaves at doses of 100 mg/kg bw, 200 mg/kg bw, and 400 mg/kg bw significantly reduced serum uric acid as compared to negative control group of carboxymethylcellulose 0.5%.

Conclusion: Ethanol extract of *S. cumini* leaves can be used as antihyperuricemic agent.

Keywords: Ethanol extract of *Syzygium cumini* leaves, Serum uric acid, Potassium oxonate.

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INTRODUCTION

Uric acid is the final metabolite of the purine catabolic pathway in humans. Hyperuricemia is a state of high uric acid levels; hyperuricemia occurs due to excessive production of uric acid or low excretion of the acid, abnormal amounts of uric acid in the body, resulting in the deposition of urate crystals in the joints and kidneys, causing inflammation as well as gouty arthritis and has been linked to renal dysfunction [1]. Epidemiological studies showed that more than 20% of the world's population suffered from gout [2].

Gout can be treated using synthetic or natural medicine. Uricosurics and uricostatics are the synthetic drugs commonly used to treat gout. Uricosuric drugs work by inhibiting the reabsorption of uric acid in the kidney tubules so the excretion of uric acid through the kidneys can be improved [3]. Uricostatics such as allopurinol is one of the most widely used synthetic medicines to inhibit the synthesis of uric acid. However, the use of allopurinol is accompanied by side effects such as allergic reactions [4]. Besides treatment with synthetic medicines, alternative measures using agents derived from plants may also be considered in helping to lower uric acid levels. This can be done while putting an effort to reduce side effects of synthetic medicines. The ability of the extract in reducing the concentration of uric acid is suspected due to the content of the flavonoid compound. Flavonoids are widely found in fruits and vegetables. One species of plant that is expected to contain flavonoid is *Syzygium cumini* [5].

Based on research that has been conducted, *S. cumini* leaves have three active flavonoid compounds which were quercetin, myricetin, and kaempferol [6]. Quercetin and myricetin are xanthine oxidase inhibitors and have free radical dampening activity; kaempferol is a xanthine oxidase inhibitor [7]. The purpose of this study was to investigate the effect of ethanol extract of *S. cumini* leaves on serum uric acid levels in rats which induced by potassium oxonate.

MATERIALS AND METHODS

Materials

The materials used in this study were potassium oxonate (Sigma-Aldrich), 0.9% saline (Widatra Bhakti), ethanol 96% (technical), and allopurinol (Kimia Farma), the reagent used was from analytical grades.

Plant material

S. cumini leaves were collected from Meuraksa, Aceh, Indonesia. The plant materials were identified by LIPI Bogor.

Preparation of extracts

S. cumini leaves were washed well, the leaves were dried at room temperature and coarsely powdered. The powder was extracted with ethanol 96% using cold percolation method.

Antihyperuricemic activity

A total of 30 male rats weighing ±170 g were used for this study. The rats were allowed to adapt to their environment at a constant temperature for a week before being used. They were given free access to feed standard pellets and water during the study. The use of animals in this study was approved by the Animal Research Ethics Committee Chairman, Faculty of Mathematics and Natural Sciences, Universitas of Sumatera Utara.

Rats were divided into six groups containing five animals in each.

- Group I: Rats were induced by potassium oxonate (250 mg/kg bw) intraperitoneally, after 1 h, rats were administered orally of ethanol extract of jamblang leaves at dose of 100 mg/kg bw.
- Group II: Rats were induced by potassium oxonate (250 mg/kg bw) intraperitoneally, after 1 h, rats were administered ethanol extract of jamblang leaves at dose of 200 mg/kg bw.
- Group III: Rats were induced by potassium oxonate (250 mg/kg bw) intraperitoneally, after 1 h, rats were administered orally of ethanol extract of jamblang leaves at dose of 400 mg/kg bw.
- Group IV: Rats were induced by potassium oxonate (250 mg/kg bw) intraperitoneally, after 1 h, rats were administered orally suspension of allopurinol (10 mg/kg bw).
- Group V: Normal group (without treatment).
- Group VI: Rats were induced by potassium oxonate (250 mg/kg bw) intraperitoneally, after 1 h, rats were administered orally of carboxymethylcellulose (CMC) 0.5%.

Each group was administered orally for 7 days. On the 8th day, rats were sacrificed by cervical dislocation for blood collection for serum uric acid measurement. Blood was collected by venous cava caudal. Serum uric acid level was measured by autoanalyzer (*Cobas integra*).

Statistical analysis

The statistically significant of difference was calculated by the analysis of variance followed by Tukey *post hoc* test. Statistically significant was set at $p<0.05$. The results were expressed as the mean ± SEM of each group.

RESULT

Potassium oxonate caused hyperuricemia in rats, as indicated by drastic increases in the serum uric acid levels in negative if control group. Serum uric acid of all groups is shown in Table 1.

Administration of the uricase inhibitor, potassium oxonate 250 mg/kg bw resulted in hyperuricemic in rats, as indicated by an increase in the serum uric acid levels negative control group (Group VI) when compared to the normal control group (Group V), proving that allopurinol may decrease uric acid levels induced by potassium oxonate. Treatment with ethanol extract of *S. cumini* leaves (I-III) significantly ($p<0.05$) reduced the serum urate levels when compared with the negative control group (Group VI). The standard drug allopurinol at dose of 10 mg/kg bw significantly ($p<0.05$) reduction of serum urate level compared to negative control group (Group VI). Ethanol extract of *S. cumini* leaves dose 400 mg/kg bw was not significantly different of serum uric acid compared with control normal group ($p>0.05$) and control positive group ($p>0.05$).

All treatment groups were significantly different from the negative control group. The negative control group was the groups which were induced with potassium oxonate 250 mg/kg bw until the rats had hyperuricemia. The percentage of uric acid in rats which compared to negative control group could be seen in Fig. 1.

The ethanol extract of *S. cumini* leaves has the ability to decrease uric acid, but it has lower efficacy compared to allopurinol. This is possible because allopurinol is a synthetic drug widely used for hyperuricemia. The results showed that ethanol extract of *S. cumini* leaves could be used as a candidate of the traditional uric acid drug.

DISCUSSION

Uric acid is the end metabolite from purine compounds (xanthine) which catalyzed by xanthine oxidase. This enzyme plays an important role in catalyzing the conversion of hypoxanthine into xanthine, then processed into uric acid. Hyperuricemia is an excess of uric acid in the blood [8]. Potassium oxonate causes hyperuricemic in rats by inhibiting the uricase activity, if the enzyme is inhibited, uric acid will accumulate in rats; therefore, elevation of uric acid seems to result from the inhibition of uric acid metabolism [9].

Allopurinol significantly prevented that elevation (Table 1). Allopurinol reduces uric acid by inhibiting xanthine oxidase which is an enzyme that plays a role in the formation of uric acid; xanthine oxidase is an essential target for pharmacology intervention in hyperuricemic or gout patients [10]. Allopurinol can also shrink the size of tophi so easily remove it from the body [9].

S. cumini leaves have two active flavonoid compounds that lower uric acid levels are quercetin and kaempferol [11]. The mechanism of action of the kaempferol inhibits xanthine oxidase by the inhibitory effects of them on xanthine oxidase activity [12]. Quercetin regulates renal organic ion transporters and uromodulin which play the important roles in renal urate excretion so that only a few uric acid is reabsorbed [13]. Based on above, so that the ethanol extract of *S. cumini* leaves can be used effectively as antihyperuricemic with an effective dose was 400 mg/kg bw.

CONCLUSION

The results of this study demonstrated the ethanol extract of *S. cumini* leaves can reduced serum uric acid level in oxonate-induced rats with an effective dose were 400 mg/kg bw.

Table 1: Effect of ethanol extract of *S. cumini* on serum urate levels in rats-induced potassium oxonate (mean±SME, n=5)

Groups	Uric acid serum (mg/dL)
S. cumini extract 100 mg/kg bw	4.68±0.35[a-c]
S. cumini extract 200 mg/kg bw	4.53±0.06[a-c]
S. cumini extract 400 mg/kg bw	3.12±0.42[c]
Allopurinol dosis 10 mg/kg bw	2.94±0.23[c]
Normal control group	2.70±0.19[c]
Negative control group	7.06±0.67[a, b]

Data were represented as mean±standard error. [a]Means significantly different compared with normal group ($p<0.05$). [b]Means significantly different compared with normal control group ($p<0.05$). [c]Means significantly different compared with control negative group received CMC 0.5% ($p<0.05$), *S. cumini: Syzygium cumini*

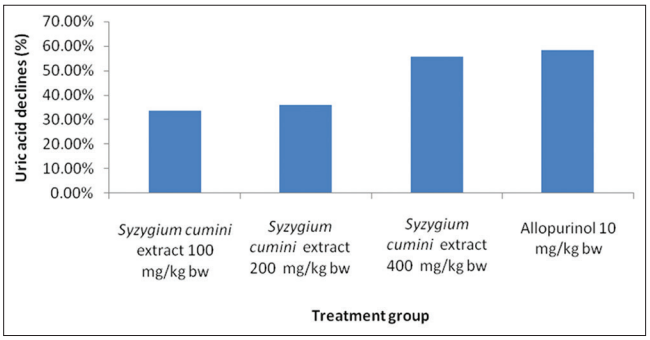

Fig. 1: Percentage of reduction of uric acid levels in all treatment groups which compare to negative control group

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AUTHOR'S CONTRIBUTIONS

Experiments, designs, assisting data interpretation, compiling, and revising proposed manuscripts assisted by R and Y. All authors reviewed and approved the contents of the manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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