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UNLOCKING THE ANTI-HYPERURICEMIA POTENTIAL OF *Arcangelisia flava* STEM: AN IN VIVO STUDY IN HYPERURICEMIC RATS

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ABSTRAK

Hiperurisemia adalah kondisi meningkatnya kadar asam urat dalam darah yang berisiko memicu gout dan gangguan metabolisme lainnya. Terapi konvensional seperti allopurinol efektif, namun memiliki efek samping, sehingga diperlukan alternatif alami yang lebih aman. Arcangelisia flava, tanaman obat tradisional, diketahui mengandung senyawa bioaktif dengan potensi antiinflamasi dan antioksidan. Penelitian ini bertujuan mengevaluasi efek anti-hiperurisemia dari ekstrak etanol batang A. flava secara in vivo pada tikus yang diinduksi kalium oksonat. Tikus dibagi dalam kelompok kontrol, model hiperurisemia, dan perlakuan dengan dosis ekstrak 100, 200, dan 400 mg/kg BB. Kadar asam urat diukur secara enzimatik sebelum dan sesudah perlakuan. Hasil menunjukkan ekstrak A. flava menurunkan kadar asam urat secara signifikan (p=0,000), terutama pada dosis 400 mg/kg BB yang menurunkan kadar asam urat hingga 74,17%. Temuan ini mendukung potensi A. flava sebagai agen anti-hiperurisemia alami.

ABSTRACT

Unlocking The Anti-Hyperuricemia Potential Of Arcangelisia Flava Stem: An In Vivo Study In Hyperuricemic Rats. Hyperuricemia is a condition of increased uric acid levels in the blood that can trigger gout and other metabolic disorders. Conventional therapies such as allopurinol are effective, but have side effects, so safer natural alternatives are needed. Arcangelisia flava, a traditional medicinal plant, is known to contain bioactive compounds with anti-inflammatory and antioxidant potential. This study aims to evaluate the anti-hyperuricemic effect of ethanol extract of A. flava stems in vivo in potassium oxonate-induced rats. Rats were divided into control groups, hyperuricemia models, and treatments with extract doses of 100, 200, and 400 mg/kg BW. Uric acid levels were measured enzymatically before and after treatment. The results showed that A. flava extract significantly reduced uric acid levels (p=0.000), especially at a dose of 400 mg/kg BW which reduced uric acid levels by 74.17%. These findings support the potential of A. flava as a natural anti-hyperuricemic agent.

INTRODUCTION

Hyperuricemia is a state of increased serum uric acid levels, usually more than 6 mg/dL in women and 7 mg/dL in men, caused by increased uric acid production, decreased excretion, or a combination of both. According to the World Health Organization (2016), men have average values of 3.5 - 7 mg/dL, and women have values of 2.6 - 6 mg/dL. Uric acid (UA) is the end product of exogenous and endogenous purine metabolism. The main metabolic sites of uric acid are in the liver

and intestines. Endogenous uric acid production is around 300 - 400 mg/day, while that from the diet is around 300 mg/day. UA is biosynthesized in the liver and excreted through the urine and in small amounts through blood and other body fluids. Biologically, UA is a powerful antioxidant that has the ability to act as an immune system stimulant. Xanthine oxidase (XO) is an enzyme that catalyses the transformation of purine-based compounds, which will oxidize hypoxanthine to xanthine and produce uric acid along with the generation of reactive oxidative species (ROS).[1–5] One-third of uric acid will be excreted in the intestine, but the majority of two-thirds of uric acid will be processed in the kidneys, filtered, and secreted, and then 90% will be reabsorbed. Increased uric acid levels in the blood can lead to the formation of urate crystals in the joints and soft tissues, which can trigger inflammation and cause joint damage.[6] Epidemiologically, the prevalence of hyperuricemia has increased significantly. Based on Riset Kesehatan Dasar Republik Indonesia (Riskesdas RI) in 2018, the prevalence of people with hyperuricemia reached 1.45% of the population in Indonesia. The increase in hyperuricemia rates is directly proportional to the rise in individual age.[7]

The drugs used to reduce serum uric acid levels are XO inhibitors, such as allopurinol, febuxostat, and topiroxostat. Allopurinol is a purine-like XO inhibitor, while febuxostat and topiroxostat are non-purine XO inhibitors. Allopurinol has side effects such as looseness, hepatitis, and interstitial nephritis. Febuxostat may cause a 2% increase in liver enzyme levels, rash, joint pain, and greater cardiovascular risk for elderly patients. Topiroxostat has side effects of mild to moderate renal impairment.[8–10] To minimize these side effects, bioactive compounds found in herbs have been explored in reducing serum uric acid levels.

Herbs that have been studied to reduce serum uric acid by inhibiting xanthine oxidase are *Teucrium polium*, *Prunus avium*, *Smilax riparia*, *Rhus coriaria*, *Foeniculum vulgare*, *Allium cepa*, *Camellia japonica*, *Helianthus annuus*, *Sonchus arvensis*, and from the Menispermaceae family are *Anamirta cocculus* and *Sphenocentrum jollyanum Pierre*.[11–13] Several secondary metabolites have been identified and isolated from herbs that are reported to have effective XO inhibitory activities, such as polyphenols, terpenoids, saponins, alkaloids, and phenylethanoid glycosides.[14] Bioactive compounds in plants such as luteolin, quercetin, isorhamnetin, galangin, chrysin, prosapogenin, cajaninstilbene acid, can inhibit the XO enzyme, the strength of which is close to or stronger than allopurinol.[15]

A flava, which belongs to the Menispermaceae family, contains secondary metabolites in the form of alkaloids, phenolics, flavonoids, saponins, tannins, and berberine.[16] The test results of *A. flava* ethanol extract in inhibiting xanthine oxidase enzyme in vitro obtained an IC_{50} of 30.44 µg/mL, with an active category in inhibiting xanthine oxidase enzyme.[17] Therefore, this study aims to evaluate the potential of the ethanolic extract of *A. flava* stem as an anti-hyperuricemia in vivo using a potassium oxonate-induced hyperuricemic rat model.

METHODS

This research was conducted in the Basic Medical Chemistry laboratory and Animal House laboratory, which was carried out from June to December 2023. This research has received a certificate of ethical worthiness with no 121-2023. This research is an in vivo experimental study with a pre-post-test and a control group research design to determine the anti-hyperuricemia properties of the ethanolic extract of *A. flava* stem.

A. flava was obtained from Lubuk Linggau city in Musi Rawas District, South Sumatra, Indonesia. The *A. flava* was determined in the Biosystematics Laboratory, Department of Biology at

the Faculty of Mathematics and Natural Sciences, Universitas Sriwijaya. The leaves and roots of *A. flava* were removed. The stem, about 2 cm or more in diameter, with the color green and the middle of the stem is yellow, was washed with running water, drained, cut into small pieces, and dried in the oven at 40^{o}Celsius. After obtaining a constant weight, the *A. flava* stem was stored in a closed container at room temperature. *A. flava* stem (3000 g) was macerated with 96% ethanol for 3 × 24 hours. The maceration was stirred several times. The macerate obtained was filtered through filter paper (Whatman 100), collected, and evaporated with a rotary evaporator until it became a thick extract.

This study used 25 male white rats (Rattus norvegicus), aged 8-10 weeks and weighing 180-235 grams. The rats were acclimatized for 7 days before the treatment began. The rats were fed a standard diet every morning and evening and given water. After acclimatization, the rats were randomly divided into five groups (n = 5 per group): negative control group, positive control group, first dose treatment group, second dose treatment group, and three types of dose treatment group. The randomization process was performed using a random number generator to ensure even distribution and avoid selection bias. To maintain objectivity, the study was conducted in a single-blind manner, where the researcher performing the outcome measurements was unaware of each rat's group allocation. Each animal was assigned a random identity code with numbers 1 to 25, and treatments were packaged in identical containers that did not indicate dose or group. Only laboratory technicians not involved in data collection were aware of the group allocation and treatment codes. After adaptation, uric acid levels are measured as average values, and rats are induced with chicken liver juice at a dose of 15 g/kgBW orally twice daily for seven days. On the seventh day, potassium oxonate in a 250 mg/kg BW dose is induced intraperitoneally, and uric acid levels are measured. Rats are classified as hyperuricemic if serum uric acid levels are >7.5 mg/dL.[18]

The male Wistar rats were divided into five groups, namely group I (negative control) was given Na-CMC 1% suspension, group II (positive control) was given allopurinol-Na-CMC 1% suspension, group III (dose of 100 mg/kg BW) was given a suspension of ethanolic extract of *A. flava*-Na-CMC 1%, group IV (dose of 200 mg/kg BW) was given a suspension of ethanolic extract of *A. flava*-Na-CMC 1%, and group V (dose of 400 mg/kg BW) was given a suspension of ethanolic extract of *A. flava*-Na-CMC1%). The rats were treated for seven days.

The blood was taken on days 0, 4th, and 7th from the ophthalmic vein located in the saccus medians orbitals in the eyes of rats using a capillary tube. After the blood came out through the capillary tube, the blood was collected in a centrifuge tube and centrifuged for 5 minutes at 5000 rpm. The separated blood serum was taken using a micropipette and put into a new tube. A total of 20 µl of serum sample was added with 1000 µl of uric acid reagent (HUMAN), mixed, and incubated at 37^{o}C for 5 minutes. After that, the absorbance was measured using a UV-Vis spectrophotometer (Shimadzu UV 1800 UV-Vis) at a wavelength of 520 nm.

To the calculate of uric acid levels, we use the following formula:

$$C = STD \times \frac{\Delta A \text{ sample}}{\Delta A \text{ STD}}$$

Description: C = Uric acid concentration
STD = Standard
ΔA sample = Absorbance of sample
ΔA STD = Absorbance of standard
Conversion Factor = 1 mg/dL = 59.485 µmol/L

Data from this study were analyzed using the Statistical Package for the Service Solution (SPSS) version 22 program. To determine the difference in uric acid levels before and after treatment, a paired t-test was conducted because the data were normally distributed. To determine the effect of ethanol extract of A. flava stem on uric acid levels in male rats and comparison of uric acid levels after treatment of each group, the one-way ANOVA test was conducted because the data were normally distributed. To determine significant differences and appropriate doses, post hoc tests were used. Because the data variance is homogeneous, the Least Significant Difference (LSD) post hoc test is used.

RESULTS

A thick extract was obtained from the maceration process of *A. flava* stem with 96% ethanol (Table 1).

Table 1. Results of the extract yield

Plant Part	Weight of Simplisia	Ethanolic Extract	Yield
Stem	3000 g	40.6121 g	1.35%

After male Wistar rats were induced into a hyperuricemia model, they were treated according to their groups. Uric acid levels were examined after treatment for 4 and 7 days. The results of the homogeneity test obtained p=0.896 (p>0.05), so it was concluded that the data on day 0 (before treatment) were homogeneous. The normality test using the Shapiro-Wilk test on days 0, 4th, and 7th, where the results obtained p>0.05, concluded that all group data were normally distributed (Table 2).

Table 2. Homogeneity and Normality Test

Treatment group	n	*Levene test*		*Shapiro-Wilk test*		
		Mean±SD	*p-value*	day-0 *p-value*	4th day *p-value*	7th day *p-value*
Negative control	5	19.68±2.30	0.896	0.104	0.411	0.185
Positive control	5	21.20±3.01		0.461	0.755	0.271
100 mg/kg BW dose	5	18.81±2.42		0.215	0.371	0.328
200 mg/kg BW dose	5	16.96±2.71		0.246	0.122	0.242
400 mg/kg BW dose	5	18.47±1.49		0.656	0.595	0.576

From the comparison of serum uric acid levels before (day 0) and after treatment (day 4 and day 7), the following significance values were obtained: Negative control group (p=0.204), which means that uric acid levels between days 0 and 7 are not significantly different, meaning that there is no decrease in uric acid levels in rats. In the positive control group (allopurinol), a dose of 100 mg/kg BW, a dose of 200 mg/kg BW, and a dose of 400 mg/kg BW of ethanol extract of A. flava stems, uric acid levels were significantly different (p<0.05). This indicates a significant decrease in uric acid levels after treatment (Table 3).

Table 3. Comparison of uric acid levels on days 0, fourth, and seventh

Uric acid level (mg/dL)		Treatment group				
		Negative control	Positive control	100 mg/kg BW dose	200 mg/kg BW dose	400 mg/kg BW dose
On day 0	**Mean±SD**	19.68±2.30	21.2±3.01	18.81±2.42	16.96±2.71	18.47±1.49
	Min-Max	18.03-23.39	16.33- 24.37	16.58-22.90	12.43-19.50	16.58-20.23
On day 4	**Mean±SD**	22.12±0.69	8.32±1.75	12.94±6.57	9.43±2.14	8.17±2.45
	Min-Max	21.50-23.13	6.47-10.86	6.01-20.58	7.86-12.95	5.31-11.09
On day 7	**Mean±SD**	21.09±1.98	6.75±0.80	7.02±1.93	7.18±1.57	4.77±0.54
	Min-Max	19.22-23.45	5.78-7.63	4.85-10.17	5.78-9.26	4.15-5.63
p-value	**day 0 and 4th**	**0.031**	**0.003**	0.055	**0.001**	**0.004**
	day 4th and 7th	0.212	**0.027**	0.063	**0.004**	**0.019**
	day 0 and 7th	0.204	**0.001**	**0.000**	**0.000**	**0.000**

After treatment for 7 days, the calculation of percentage reduction in uric acid in Table 4 helps interpret the biological relevance, which complements the statistical significance. It was seen that the treatment group with allopurinol and the three doses of extracts were able to reduce uric acid levels by>50%, while the negative control group did not experience a decrease in uric acid levels because this group was only given 1% Na-CMC. Of the treatment groups that experienced a reduction in uric acid levels, it was seen that the 400 mg/kg BW dose group had the most significant difference of 74.17%. The 200 mg/kg BW dose group had the slightest difference of 57.66%. (Table 4).

Table 4. Difference in Uric Acid Level

Treatment Group	Uric Acid level on day 0 (mg/dL)	Uric Acid Level on the 7th day (mg/dL)	Difference Mean	Difference (%)
	Mean±SD	Mean±SD		
Negative control	19.69±2.30	21.09±1.98	-1.40	-7.11%
Positive control	21.20±3.01	6.75±0.80	14.45	68.16%
100 mg/kg BW dose	18.81±2.42	7.02±1.93	11.79	62.67%
200 mg/kg BW dose	16.96±2.71	7.18±1.57	9.78	57.66%
400 mg/kg BW dose	18.47±1.49	4.77±0.54	13.70	74.17%

A comparison of uric acid levels during observation in rats before (day 0) and after treatment (fourth and seventh day) shows differences in serum uric acid levels in the negative control group compared with the positive control group and the treatment groups (Figure 1).

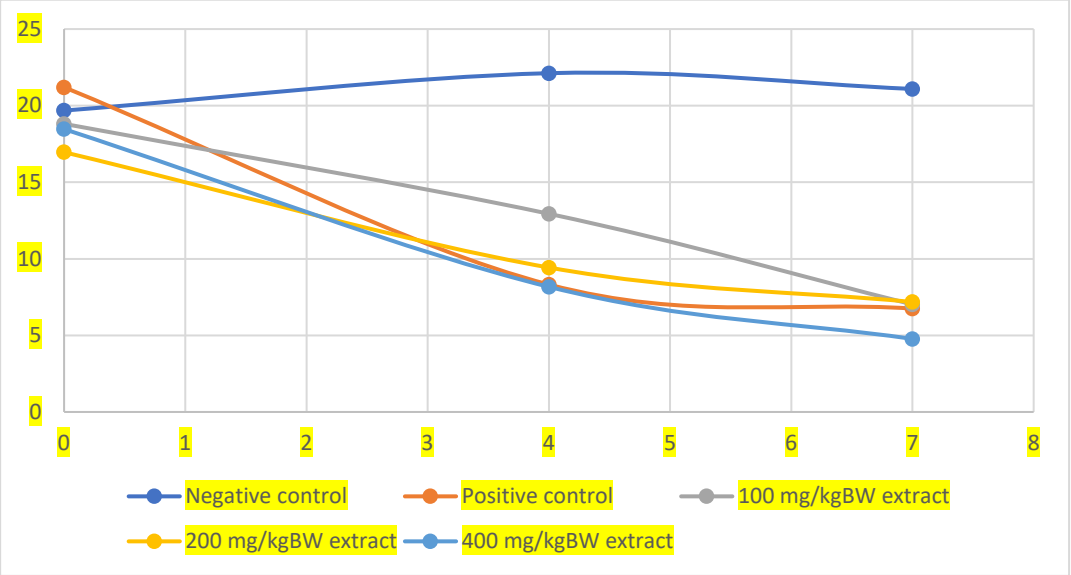

Figure 1. Comparison of uric acid levels among groups

Based on the One-way ANOVA test on the seventh day, the significance value between treatment groups was p=0.000 (p>0.05), meaning there was a significant difference between treatment groups in reducing uric acid levels in rats on the seventh day. Data analysis conducted to determine differences in the decrease in uric acid levels of each group compared to the positive control group is a post hoc test using the Least Significant Difference (LSD). The results of the LSD test for the determination of the efficacy of the dose obtained are as follows: 100 mg/kg BW and 200 mg/kg BW doses compared to positive control are equally effective in reducing uric acid levels, but doses of 100 and 200 mg/kg BW are significantly different from 400 mg/kg BW dose which 400 mg/kg BW dose is more effective in reducing uric acid levels. However, 100 mg/kg BW doses reduce uric acid levels (Table 5).

Table 5. Statistical Analysis of Uric Acid Level on Day 7 using Post-hoc LSD Test

Group		*p-value*
Positive control	Negative control	**0.000**
100 mg/kg BW	200 mg/kg BW	0.866
	400 mg/kg BW	**0.027**
	Positive control	0.776
	Negative control	**0.000**
200 mg/kg BW	400 mg/kg BW	**0.019**
	Positive control	0.651
	Negative control	**0.000**
400 mg/kg BW	Positive control	**0.049**
	Negative control	**0.000**

DISCUSSION

Studies on the ethanolic extract of *A. flava* stem have anti-hyperuricemia effects through mechanisms such as inhibition of xanthine oxidase and increased uric acid excretion. This research, using the ethanolic extract of *A. flava* stem in doses of 100 mg/kg BW, 200 mg/kg BW, and 400

mg/kg BW for seven days, showed that there was a decrease in serum uric acid levels in hyperuricemia conditions in male Wistar rats. Hyperuricemia conditions in this study sample were due to induction with chicken liver juice 15 g/kg BW for seven days and induction with 250 mg/kg BW potassium oxonate intraperitoneally.[19–21] In rats, uric acid levels are 1.2- 7.5 mg/dL. The rats were categorized to have hyperuricemia if uric acid levels were ≥ 7.5 mg/dL.[18] Rats were induced orally with chicken liver juice 15 g/kg BW for seven days and with potassium oxonate 250 mg/kg BW intraperitoneally.[22–24] Chicken liver is a source of purines, containing 150-1000 mg/100 grams of purines synthesized into uric acid. Potassium oxonate is a competitive inhibitor of the uricase enzyme that inhibits the formation of allantoin compounds readily excreted in the rat's body, so that uric acid levels can increase rapidly. Combining increased purine production and uric acid elimination inhibitors induces hyperuricemia.[25]

Chicken liver contains high purine levels, so it can be used as a raw material to form uric acid. Potassium oxonate can inhibit the uricase enzyme that converts xanthine to allantoin, so that serum uric acid levels in rats increase.[26,27] All groups are in hyperuricemia, meaning chicken liver juice and potassium oxonate as uricase enzyme inhibitors successfully increase uric acid levels in rats.[27]

The results on days 0 and 7 showed significant differences in the positive control group, 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW dose groups. Still, there was no significant difference in the negative control group because the negative control group was given Na-CMC, which has no effect in reducing uric acid levels, so from day to day, uric acid levels increased, while the positive control group given allopurinol by 100 mg can significantly reduce uric acid levels because allopurinol as the first line in the treatment of hyperuricemia is a competitive xanthine oxidase inhibitor that will be converted into oxypurinol so that it can be excreted through the kidneys, resulting in inhibition in uric acid biosynthesis and uric acid levels decrease.[27]

The treatment given to the group of ethanolic extract of *A. flava* stem can reduce uric acid levels in rats. Meanwhile, based on the LSD post-hoc test, it was found that the doses of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW were effective in reducing uric acid levels, just like allopurinol. Still, the 400 mg/kg BW dose was more effective in lowering the uric acid levels of the three doses. Based on descriptive tests, the percentage difference between the dose of 400 mg/kg BW (74.17%) has more potential to reduce uric acid than the dose of 100 mg/kg BW (62.67%) and 200 mg/kg BW (57.66%).

There was a decrease in uric acid levels greater than 50% in favorable control doses of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW. This is in line with research conducted previously, which states that the test of ethanolic extract of *A. flava* stem based on phytochemical results can inhibit the enzyme xanthine oxidase with an IC_{50} of 30.44 µg/mL, which is an active category in inhibiting the enzyme xanthine oxidase. In *A. flava* stem, there is a secondary metabolite content in flavonoids, potent inhibitors of xanthine oxidase activity on purine bases to reduce uric acid levels.[17,28]

Flavonoids can reduce uric acid by inhibiting xanthine oxidoreductase (XOR) and modulating uric acid transporters such as GLUT9, URAT1, and OAT1/3. Several studies have consistently confirmed that the anti-hyperuricaemic properties of herbs are due to the presence of various physiologically active substances, especially polyphenolic compounds. These polyphenolic compounds can inhibit uric acid production and increase renal uric acid excretion while preventing uric acid reabsorption in the kidney. It is also explained that polyphenolic compounds have anti-hyperuricemia abilities comparable to synthetic drugs such as allopurinol.[29] Flavonoids are derived from polyphenols and have fifteen carbon atoms in the C6-C3-C6 configuration. This compound is a

group of chemical compounds found naturally in plants because it includes polyphenolic compounds; flavonoids have a benzene ring structure with a bound carbon ring.[24] Flavonoid compounds can act as inhibitors; hydroxyl and carbonyl groups will form hydrogen bonds in inhibitor interactions on the active side of the XO enzyme.[30] Anthocyanins and flavones are the fundamental structures of flavonoid compounds that increase uric acid excretion through the kidneys by inhibiting the expression of GLUT9 and URAT1. Flavone compounds include apigenin and baicalein. The mechanism of action of apigenin, by inhibiting the expression of GLUT9 and URAT1 in hyperuricemia conditions in rats, can also inhibit xanthine oxidase activity, decreasing blood uric acid levels. Baicalein inhibits the expression of GLUT9 and URAT1 in the kidneys to increase uric acid excretion and reduce uric acid levels in hyperuricemia rats.[31]

Other compounds can reduce uric acid levels in the form of alkaloids and tannins. In the phytochemistry test, the ethanolic extract of *A. flava* stem has alkaloids. Alkaloids are a group of chemical compounds found naturally in various organisms, especially plants. They generally have nitrogen-based structures and pharmacological solid effects in humans and animals; these compounds are the most nitrogen-containing.[32] Alkaloids can also be xanthine oxidase inhibitors by inhibiting the enzyme's work. One of the alkaloid compounds, colchicine, can degrade xanthine. The potential of alkaloids in reducing uric acid is because they can inhibit the activity of xanthine oxidase and adenosine deaminase, increase uric acid excretion, and block uric acid reabsorption.[33] Tannin is also included in the category of polyphenolic compounds and can form complex compounds together with proteins. Tannin compounds have a variety of chemical structures and variations in functionality. Some examples of common tannin compounds include gallate tannins, ellagite tannins, and catechin tannins.[34] Further research can be carried out on isolating compounds contained in the ethanolic extract of *A. flava* for xanthine oxidase inhibition, both in vitro and in vivo.

CONCLUSION

Ethanol extract of *A. flava* stem has the potential as an anti-hyperuricemia because it can reduce uric acid levels in the hyperuricemia rat model induced with potassium oxonate, and with a dose of 100 mg/kgBW already capable of reducing serum uric acid levels.

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