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Potential of Anti-hyperuricemia Effect Ethyl Acetate Extracts from *Arcangelisia flava* Stems in Model Rats

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Abstract

Hyperuricemia is a condition characterised by elevated levels of uric acid in the blood, and if chronic, can lead to gouty arthritis. The treatment for hyperuricemia is allopurinol, but many people use herbal remedies for daily use. *Arcangelisia flava* contains alkaloids, flavonoids, triterpenes, and tannins, and in vitro tests have demonstrated its effectiveness as an anti-hyperuricaemic agent. This study aims to determine the effect of ethyl acetate extract from *A. flava* stems in reducing uric acid levels in rats. This was an in vivo experimental study with a pre-post-test, randomized control group design using male white rats (n = 25) in a hyperuricemia condition, administered chicken liver juice twice daily for seven days, and induced by potassium oxonate (250 mg kg^{-1} BW) intraperitoneally. Mice were administered ethyl acetate extract from *A. flava* stems or standard medication for seven days. Blood samples were collected through the ocular vein for analysis. Uric acid levels were measured on days 0, 4, and 7 using a spectrophotometric method with uric acid reagents. Data were analysed using ANOVA and post-hoc Games-Howell tests. Administration of an ethyl acetate extract of *A. flava* stems at all doses for 7 days significantly reduced serum uric acid levels in rats (p = 0.000), with a percentage reduction in uric acid levels of more than 50% from the initial hyperuricemic condition. Based on statistical analysis, a dose of 100 mg kg-1 BW was effective. The ethyl acetate extract of *Arcangelisia flava* stems has potential as an anti-hyperuricemic agent.

***Keywords*:** *Arcangelisia flava, anti-hyperuricemic, uric acid, ethyl acetate extract*

Abstrak

Potensi Efek Anti Hiperurisemia dari Ekstrak Etil Asetat Batang Arcangelisia flava pada Tikus Model. Hiperurisemia adalah kondisi peningkatan asam urat dalam darah, dan jika terjadi secara kronis, dapat menyebabkan gout artritis. Pengobatan hiperurisemia adalah allopurinol, namun banyak orang menggunakan obat herbal untuk penggunaan sehari-hari. *Arcangelisia flava* mengandung alkaloid, flavonoid, triterpen, dan tanin, dan dalam uji in vitro, telah terbukti efektif sebagai anti-hiperurisemia. Penelitian ini bertujuan untuk menentukan efek ekstrak etil asetat batang *A. flava* dalam menurunkan kadar asam urat pada tikus. Penelitian eksperimental in vivo dengan desain kelompok kontrol acak pra-pasca-tes menggunakan tikus putih jantan (n = 25) dalam kondisi hiperurisemia, dengan pemberian jus hati ayam dua kali sehari selama tujuh hari, dan diinduksi oleh kalium oksonat (250 mg kg^{-1} BB) secara intraperitoneal. Tikus diberi ekstrak etil asetat dari batang *A. flava* atau obat standar selama tujuh hari. Sampel darah dikumpulkan melalui vena okular untuk analisis. Pengukuran kadar asam urat dilakukan pada hari ke-0, 4, dan 7 secara spektrofotometrik menggunakan reagen asam urat. Data dianalisis menggunakan uji ANOVA dan post-hoc Games-Howell. Pemberian ekstrak etil asetat batang *A. flava* pada semua dosis selama 7 hari dapat menurunkan kadar asam urat serum pada tikus dengan perbedaan yang signifikan (p=0,000), dengan persentase penurunan kadar asam urat lebih dari 50% dari kondisi awal hiperurisemia, dan berdasarkan analisis statistik, dosis 100 mg kg-1 BB merupakan dosis yang efektif. Ekstrak etil asetat batang Arcangelisia flava memiliki potensi sebagai agen anti-hiperurisemia.

Kata Kunci: *Arcangelisia flava, anti-hiperuricemia, asam urat, ekstrak etil asetat*

Introduction

Hyperuricemia is characterized by increased serum uric acid concentration in the blood, where the serum uric acid (SUA) concentration in men is ≥7 mg dL^{-1} and in women is ≥6 mg/dL. Hyperuricemia is considered a risk factor for the occurrence or development of diseases such as diabetic nephropathy, acute kidney injury (AKI), chronic kidney disease, cardiovascular disease, hypertension, and metabolic syndrome.[1-3] The prevalence of hyperuricemia is increasing rapidly in the global population. The increasing prevalence of lifestyle-related hyperuricemia is not only in developed countries but also in low- and middle-income countries.[4] Based on the Basic Health Research (Riskesdas) in 2018, the prevalence of joint disease in Indonesia, as diagnosed by a doctor, in the population aged 15 years and above was 7.3%. This prevalence increases with increasing age.[5]

The first line of hyperuricemia management is the use of xanthine oxidase inhibitors, including allopurinol and febuxostat. These drugs work by inhibiting the xanthine oxidase enzyme, reducing uric acid production.[1, 6] Therapy to reduce high uric acid levels can be achieved by reducing the production of uric acid from its precursor, thereby disrupting purine metabolism and preventing the formation of uric acid. This inhibition is divided into three types: based on mechanism (acting through interaction with the molybdenum (Mo) core, such as allopurinol), based on structure (by filling the XO enzyme channel leading to the Mo core, such as in febuxostat and Y-700), and hybrid types (interacting with the Mo core and blocking the Mo enzyme channel, such as FYX-051).[7] Currently, with a growing desire to reconnect with nature, many people are turning to traditional medicine derived from herbs. Natural medicines derived from plants are being increasingly developed because they contain secondary metabolites that are beneficial to health. Approximately 100,000 secondary metabolite compounds have been isolated and identified, and have been used as active ingredients in medicine, as well as the basis for the development of synthetic medicinal products. Therefore, research and development of plants with pharmacological properties as an alternative to medicine is needed.[7-9]

Indonesia has approximately 7,000 of the 30,000 plant species that may have medicinal properties.[10] *Arcangelisia flava* is one of the plants with medicinal properties, and many grow in the province of South Sumatra. This plant is widely used as a traditional medicine in Southeast Asia. Local people use it for the treatment of several diseases, such as malaria, dysentery, fever, abortion, hepatitis, and indigestion. In addition, *A. flava* is used to treat jaundice, smallpox, eye pain, aphthae, athlete's foot, and antihelminthic. The *Arcangelisia* genus has contents such as alkaloids, diterpenoids, and other chemical components that have antibabesial, antimicrobial, anti-inflammatory, antioxidant, antimalarial, anti-diabetic, antitumor, cardiotonic, and anti-hypertensive functions.[11, 12]

Based on the results of previous research, the results of phytochemical analysis of *A. flava* stems were obtained in the form of secondary metabolite content, such as alkaloids, flavonoids, saponins, triterpene, and tannins.[13] Several in vitro studies reported that flavonoids are potent inhibitors of xanthine oxidase activity on purine bases to reduce uric acid levels.[14] Previous research has conducted an inhibition test of the ethyl acetate extract of *A.flava* stems obtained an IC_{50} value of 23.99 ppm with a powerful category of xanthine oxidase enzyme inhibition effect.[15] In vivo studies are needed to determine the effect of ethyl acetate extract administration on reducing uric acid levels in hyperuricemic model animals. Therefore, this study aims to determine the effect of *A. flava* stems ethyl acetate extract in reducing uric acid levels in male wistar rats (*Rattus norvegicus*) with hyperuricemia.

Experimental Section

Materials and Apparatus

Arcangelisia flava stems were obtained from Lubuk Linggau City, Musi Rawas Regency, South Sumatra Province, Indonesia, and have been determined at the Biosystematics Laboratory, Chemistry Department,

Faculty of Mathematics and Natural Sciences, Sriwijaya University, male white rats (*Rattus norvegicus*), and filter paper. The chemicals used were technical ethyl acetate, chicken liver juice, potassium oxonate, distilled water, sodium carboxymethyl cellulose (Na-CMC), allopurinol, and uric acid reagent (HUMAN).

The apparatus used in this study included a macerator, glassware, oven, analytical and digital balance, rotary evaporator, animal cages with food and drink containers, oral sonde, syringe, micropipette, capillary tube, centrifuge, and a Shimadzu UV-1800 UV-Vis spectrophotometer.

A. flava Stems Extraction

A total of 3,000 grams of *A. flava* stems simplicia was extracted with ethyl acetate by maceration for three repetitions of 24 hours each. The filtrate obtained from the maceration results was evaporated using a rotatory evaporator and dried to obtain the ethyl acetate extract pasta (EEAAf).

Phytochemical Screening

The resulting extract was analyzed for its phytochemical constituents (flavonoids, alkaloids, saponins, tannins, steroids, and terpenoids) using standard qualitative methods[16].

Experimental Animal Treatments

Twenty-five male white rats aged 2-3 months, weighing 150-250 grams, were induced with chicken liver juice 15 g kg^{-1} BW orally two times a day for seven days, and on the seventh day, the rats were injected with potassium oxonate 250 mg kg^{-1} BW intraperitoneally. One hour later, blood samples were taken through the ophthalmic vein, located in the saccus medians orbitals of the rats' eyes, and uric acid levels were measured. If the uric acid level is >7.5 mg/dL, the rat is already in the hyperuricemia category. Furthermore, the rats were divided into five groups and given treatment for 7 days according to the group, namely:

1. Negative control = Na-CMC 1%
2. Positive control = Allopurinol (1.8 mg day^{-1})
3. Dose I EEAAf = 100 mg kg^{-1} BW
4. Dose II EEAAf = 200 mg kg^{-1} BW
5. Dose III EEAAf = 400 mg kg^{-1} BW

Measurement of serum uric acid levels

Serum uric acid levels were measured before and after treatment (day 0), (day 4 and day 7). Blood samples were collected using a capillary tube and then placed in a centrifuge tube. Afterward, they were centrifuged at 5,000 rpm for 5 minutes. Twenty microliters of serum samples were added to 1,000 µL of HUMAN brand uric acid reagent, mixed, and incubated at 37 °C for 5 minutes. Spectrophotometric measurements were then taken at a wavelength of 520 nm. After getting the absorbance value, manually calculate the uric acid concentration using equation (1).

$$C = STD \times \frac{\Delta A\ sample}{\Delta A\ STD} \quad (1)$$

Description:

C	= Uric acid concentration
STD	= Standard
ΔA sample	= Absorbance of sample
ΔA STD	= Absorbance of standard

The data obtained from this study will be processed using the Statistical Package for the Social Sciences (SPSS) version 22 and Microsoft Excel.

Results and Discussion

From 3 kg of *A. flava* stem simplisia extracted with ethyl acetate, 3.33 g (2.3%) of ethyl acetate extract in pasta form will be obtained.

Phytochemical Screening of A. flava

The ethyl acetate extracts of *A. flava* stems were analyzed using phytochemical tests to determine the secondary metabolites contained therein. The results of the phytochemical test are shown in Table 1.

Table 1. Phytochemical Screening

Test type	Result
Alkaloids	+
Flavonoids	+
Saponins	-
Tannins	+
Triterpenoids	+
Steroids	-

Phytochemical analysis of EEAAf contains secondary metabolites in the form of flavonoids, tannins, alkaloids, and terpenoids, and previous in vitro tests found that EEAAf can inhibit xanthine oxidase with an IC_{50} value of 23.99 ppm.[13, 17] From several studies, it was found that in *A. flava*, there are alkaloids, tannins, steroids, and alkaloids[18], alkaloids, glycosides, flavonoids, tannins, saponins, and steroids.[19]

Based on previous research, secondary metabolite compounds contained in EEAAf are flavonoids that can reduce excessive uric acid levels by inhibiting xanthine oxidoreductase (XOR) and regulating uric acid transporters such as GLUT9, URAT1, and OAT1/3.[20-22] There are two compounds from the flavonoid group, namely fisetin and hesperitin, which were tested for XO inhibition, where fisetin (IC_{50}, 0.140 mM) was superior to hesperitin (IC_{50}, 0.635 mM). From molecular docking for the combination mode of this compound with XO, the bond energy between XO and fisetin (-8.45 kcal mol^{-1}) and with hesperitin (-8.03 kcal mol^{-1}). The negative value of this bond energy indicates that the reaction occurs spontaneously. Fisetin can form 8 hydrogen bonds with XO residues, namely Ser1080, Met1038, Gly1260, Thr1083, and Val1259, while hesperitin can form 6 hydrogen bonds with XO residues, namely Phe798, Ser1080, Gln1040, Lys1045, and Thr1083. The hydrophobic interaction between fisetin and XO is stronger than that between hesperitin and XO. This is in accordance with the thermodynamic measurements that have been carried out, namely, fisetin has a DH^0 of 106.97 kJ mol^{-1}, DG^0 of 28.64 kJ mol^{-1}, and DS^0 of 437.22 J mol^{-1} K^{-1}, while hesperitin has a DH^0 of -39.85 kJ mol^{-1}, DG^0 of -25.89 kJ mol^{-1}, and DS^0 of -45.03 J mol^{-1} K^{-1}.[23]

Several bioactive compounds that have been tested for reducing uric acid levels are from the flavonoid group, namely myricetin, puerarin, and quercetin; alkaloids, namely evodiamine, betaine, tropane alkaloids hyoscyamine, scopolamine, costinones A, indirubin, berberine, apparicine, conolobine A, conolobine B, taberdivarine G, 10-hydroxyheyneanine, vobasine, pandoline, and conophylline; saponins, namely ilexsaponin C, prosapogenin, smilaxchinoside, pallidifloside D, riparoside B, and timosaponin J; triterpenoids, namely nor-oleanane triterpenoids, brachyantheraoside A3, brachyantheraoside A1, 3-O-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl-30-norolean-12,20(29)-dien-28-oic acid, brachyantheraoside D1, and brachyantheraoside B4.[7, 24, 25]

Measurement of Serum Uric Acid Levels in Rats

The use of wistar rats (*Rattus norvegicus*) in this animal study was due to their physiological, anatomical, pathological, and metabolic similarities to humans, while male animals were used because male rats have better hormonal stability than female rats, and male rats do not have estrogen hormones, as the presence of estrogen hormones can increase uric acid excretion through urine, which can cause bias in the study.[15, 26]

Rats were induced with chicken liver juice 15 g kg^{-1} BW orally for seven days, and potassium oxonate 250 mg kg^{-1} BW intraperitoneally.[27-29] Rats were considered hyperuricemic if serum uric acid levels were ≥7.5 mg dL^{-1}.[30] Chicken liver is a source of purines, containing 150-1,000 mg for 100 grams of purines synthesized into uric acid.[31, 32] Potassium oxonate is a competitive inhibitor of the uricase enzyme that inhibits the formation of allantoin compounds readily excreted in the rat body, so that uric acid levels can increase rapidly. Combining increased purine production and uric acid elimination inhibitors successfully induces hyperuricemia.[32] Following this induction, all rats became hyperuricemic, with an average uric acid level of 18.57 $\pm$ 2.63 mg dL^{-1}.

Administration of three doses of EEAAf and allopurinol orally to these hyperuricemic model rats can reduce their uric acid levels over time, whereas the negative control group, which did not receive treatment, did not experience a decrease in uric acid levels. This can be observed from the measurement of serum uric acid levels after the rats were induced into a hyperuricemia model and had not yet received treatment (day 0), and after treatment on days 4 and 7. The results are presented in Table 2 and Figure 1.

Table 2. Serum Uric Acid Level During Treatment

Treatment groups	Mean ± SD of serum uric acid levels (mg $dL^{-1)}$		
	Day 0	Day 4	Day 7
Negative control	19.69 ± 2.30	22.12 ± 0.69	21.09 ± 1.98
Positive control	21.20 ± 3.01	8.32 ± 1.75	6.75 ± 0.80
Dose I EEAAf	16.81 ± 2.01	7.81 ± 1.36	5.45 ± 1.46
Dose II EEAAf	17.90 ± 1.31	10.86 ± 2.69	7.39 ± 2.23
Dose III EEAAf	17.25 ± 2.14	9.34 ± 1.94	4.32 ± 0.31

Research on the ethanol extract of Sembukan leaf (*Paederia foetida* L.) has shown that it can reduce uric acid levels in white rats (*Rattus norvegicus*). It was thought to be related to the flavonoid content in the extract, which can competitively inhibit xanthine oxidase and superoxidase enzymes, thereby reducing uric acid levels in the blood. Flavonoid compounds can act as antioxidants by donating their electrons to oxygen, thereby preventing the reaction of xanthine substrates with oxygen and the subsequent formation of uric acid.[33] From the research on the antioxidant activity of daruju leaf extract (*Acanthus ilidifolius* L.), it is found that the phenol content contained in ethyl acetate and ethanol extracts, but not in hexane extracts, affects the percent inhibition and IC_{50} values obtained.[34] This antioxidant can also function as an anti-inflammatory agent. For example, in research, the anti-inflammatory test of the ethyl acetate fraction of fragrant pandanus root (*Pandanus amaryllifolius* Roxb.) on carrageenan-induced mice leg edema found that the ethyl acetate fraction had the best anti-inflammatory activity compared to other fractions.[35]

Uric acid levels were tested using the Shapiro-Wilk distribution on days 0, 4, and 7 for each test group, with a p-value > 0.05, indicating that the data from all groups were normally distributed. The homogeneity test on day 0 obtained $p < 0.05$ and showed that the data were homogeneous. Furthermore, the meaningfulness of the decrease in uric acid levels was analyzed compared to the time before treatment (day 0) using the paired T-test; it was found that there was a significant difference ($p < 0.05$) in the decrease in uric acid levels compared to the beginning of treatment in the positive control group and all EEAAf dose groups. Meanwhile, the negative control showed no difference in reducing uric acid levels ($p > 0.05$).

On the seventh day, the positive control group and the EEAAf dose group were able to reduce serum uric acid levels by more than 50%. The mean difference in serum uric acid levels and the percentage difference

showed a greater reduction with longer treatment. Comparative data on the mean serum uric acid levels and percentage differences from day 0 to day 4, and from day 0 to day 7, for each treatment group are presented in Table 3.

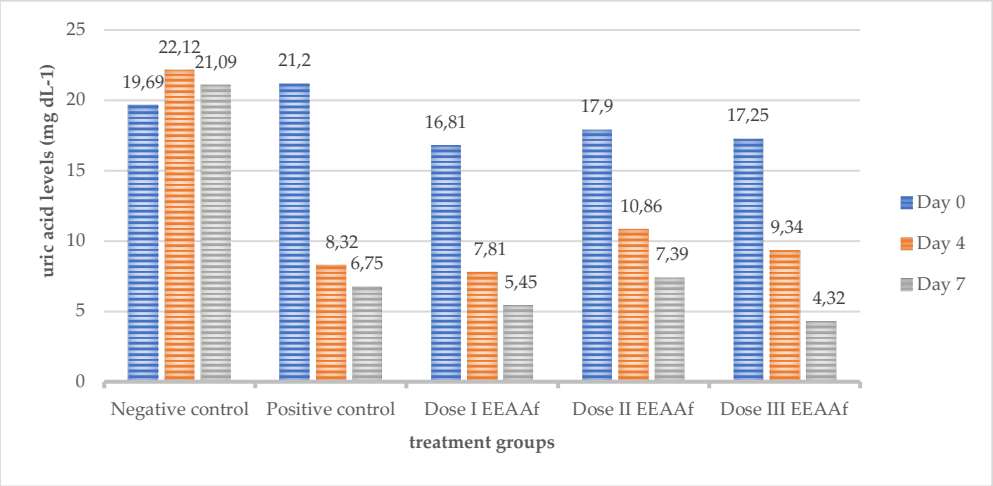

Figure 1. Comparison of Uric Acid Levels During Seven Days of Treatment

Table 3. The Comparison of Mean Serum Uric Acid Levels

Treatment groups	day 0 and day 4			day 0 and day 7		
	p-value	mean difference	difference (%)	p-value	mean difference	difference (%)
Negative control	0.031*	-2.43	-12.34	0.204*	-1.4	-7.11
Positive control	0.003*	12.88	60.75	0.001*	14.45	68.16
Dose I EEAAf	0.000*	9.00	53.54	0.000*	11.36	67.57
Dose II EEAAf	0.003*	7.04	39.33	0.000*	10.51	58.71
Dose III EEAAf	0.003*	9.91	57.45	0.000*	12.93	74.95

**paired T-test* ($p<0.05$)

Table 4. Effectiveness Test with *Games-Howell*

Treatment groups		*p-value*
Positive control	Negative control	0.000
Dose I EEAAf	Dose II EEAAf	0.528
	Dose III EEAAf	0.525
	Positive control	**0.481**
	Negative control	0.000
Dose II EEAAf	Dosis III EEAAf	0.151
	Positive control	**0.968**
	Negative control	0.000
Dose III EEAAf	Positive control	**0.007**
	Negative control	0.000

The one-way ANOVA test conducted revealed significant differences between treatment groups in reducing serum uric acid levels, with a p-value of 0.000. Test for differences between treatment groups using the *Games-Howell* post hoc test in Table 4. The positive control groups, dose I EEAAf, dose II EEAAf, and dose III EEAAf, compared to the negative control, obtained a value of $p < 0.05$, indicating a significant difference between the groups and the negative control. For the EEAAf dose I group and EEAAf dose II compared to the positive control, a p-value of>0.05 was obtained, indicating that there is no significant difference in the anti-hyperuricemia effect. This suggests that EEAAf can reduce uric acid levels, similar to allopurinol, the positive

control. Based on the data from Table 3 and Table 4, it can be concluded that dose I EEAAf (100 mg kg-1 BW) is more effective than dose II EEAAf.

Conclusions

The ethyl acetate extract of the *Arcangelisia flava* stems can reduce serum uric acid levels in hyperuricemic male white rats, with a dose of 100 mg kg-1 BW effectively reducing uric acid levels.

Conflict of Interest

The author declares that they have no conflict of interest that could have appeared to influence the work in this paper.

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