

Dose Optimization of Antihyperuricemia Effects of Matoa Leaf (*Pometia pinnata* J.R.Forst & G.Forst) in Rats

Nurul Afiah*, Irma Santi, Bayu Putra

Laboratory of Biopharmacy & Pharmacology, Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar 90231, Indonesia

*Corresponding Author. Email: nurulafhah@gmail.com

Received: 29 May 2023 / Revised: 10 June 2023 / Accepted: 25 July 2023

ABSTRACT: Hyperuricemia is a condition of increased uric acid levels in the blood above normal limits that can cause pain or soreness, which if not treated immediately will cause chronic gout, the formation of tofus, and severe kidney function disorders. One plant that is thought to have anti-hyperuricemia effects is matoa leaves (*Pometia pinnata* J.R.Forst & G.Forst) because they contain secondary metabolite compounds, namely flavonoids. This study is an experimental study using 25 male white rats divided into 5 treatment groups, namely group I (Na-CMC, negative control), group II (Allopurinol, positive control 100 mg), group III, IV, and V were given matoa leaf ethanol extract (EEDM) with successive doses of 200 mg/kg body weight (BW), 400 mg/kg BW, and 800 mg/kg BW for 4 days. Test animals were induced with fresh chicken liver juice orally for 7 consecutive days and potassium oxonate 250 mg/kg BW intraperitoneally on day 8. On the 9th to 12th day, EEDM therapy was carried out. Measurement of uric acid levels was carried out on days 0 (before treatment), 7, 8, and 12. The data were then processed statistically using *Kruskal-Wallis* and the *Mann-Whitney follow-up* test. From the results of the study, it can be concluded that ethanol extract of matoa leaves has an effect as anti-hyperuricemia with the most effective dose being 200 mg/kg BW.

KEYWORDS: Anti-hyperuricemia; extract; *Pometia pinnata*.

1. INTRODUCTION

Hyperuricemia is a condition that describes an increase in the concentration of uric acid in the body. High uric acid levels in the blood above normal cause pain or burning (Kusuma et al., 2014). Hyperuricemia is a condition of (10%) formation of uric acid levels or (90%) excretion of uric acid, and a combination of the two (Badulescu et al., 2014). However, when uric acid levels exceed normal (hyperuricemia), gout will occur which, if not treated immediately, this disease develop into chronic uric acid, forms tofus, and can cause severe kidney dysfunction and decreased quality of life (Madoni, 2017; Lallo, 2018).

The prevalence of hyperuricemia has increased worldwide in developed and developing countries (Indrawan et al., 2017). According to Riskesdas (2018), the prevalence of joint disease in Indonesia is 7.30%, while in South Sulawesi, especially Makassar, the prevalence of hyperuricemia is 6.04% in women and 4.63% in men.

One drug that is still used to reduce uric acid levels is allopurinol. Allopurinol is still commonly used in several countries, including Indonesia. Allopurinol is a drug that lowers uric acid levels by affecting the formation of purines into uric acid, which prevents uric acid crystals from forming (Imbar et al., 2019). The use of allopurinol can cause side effects; therefore, people turn to herbal medicine because it has several benefits. First, the side effects that exist in herbal plants are relatively small if used correctly, with the right dose, time, and purpose. Second, medicinal plants have complementary or synergistic factors (Harefa, 2020).

The use of plants as medicinal ingredients is closely related to the content of chemical compounds in these medicinal plants, namely the active compounds contained therein (Fawwaz et al., 2023). Matoa plant (*Pometia pinnata* J.R.Forst & G.Forst) contains metabolites of alkaloids, saponins, tannins, flavonoids, phenolics, and terpenoids as well as nutritious vitamins A, C, and E boost the immune system (Hamzah et al., 2021). Based on the description above, research will be carried out with the aim of determining the anti-hyperuricemia effects of matoa leaf ethanol extract (EEDM) in white male rats (*Rattus norvegicus*) to add scientific data on the efficacy of medicinal plants.

2. EXPERIMENTAL SECTION

This research was conducted in an experimental laboratory. The parameters observed were uric acid levels in rats as test animals. This research was conducted at the Biopharmaceutical Laboratory of the Faculty of Pharmacy, Indonesian Muslim University Makassar. The population used in this study was the matoa plant obtained from Sorong City, West Papua.

2.1. General

The tools used in this study were aluminum foil, stirring rod, stretcher spoon, iron spoon, glass funnel (Pyrex[®], Japan), beaker (Pyrex[®], Japan), measuring cup (Pyrex[®], Japan), measuring flask (Pyrex[®], Japan), porcelain dish, sterile scissors, mortar and pestle, parchment paper, digital scales (Starco BCE8), mouse oral sonde, uric acid measuring device (Nesco[®] MultiCheck). The materials used in this study were matoa leaves, male rat test animals, chicken liver juice,

potassium oxonate, allopurinol (Merck, Germany), aquadest, 96% ethanol, Na-CMC 1%, and uric acid strips (Nesco®*MultiCheck*).

2.2. Methods

A total of 25 rats were divided into 5 groups, each consisting of 5 rats. Group I was negative control given Na-CMC 1%, group II was positive control (allopurinol) with a dose of 100 mg/kg body weight (BW), group III, IV, and V were an EEDM treatment with a dose of 200, 400, 800 mg/kg BW. An initial measurement (T0) of uric acid levels was carried out using the Nesco® *MultiCheck* strips. Induction of hyperuricemia by giving chicken liver juice orally to test animals for 7 consecutive days. On the 8th day, potassium oxonate was induced with a dose of 250 mg/kg BW intraperitoneally with an administration volume of 2 mL/200 g BW. EEDM therapy was carried out on day 8 (2 hours after measuring uric acid levels) until day 12. Measurement of uric acid levels was carried out 2 hours after induction of potassium oxonate on days 0, 7, 8, and 12.

3. RESULTS AND DISCUSSION

The method used in this study was to measure uric acid levels in rats using the Nesco® *MultiCheck* tool. Chicken liver juice was induced orally through the mouth of rats for 7 consecutive days and potassium oxonate was intraperitoneal. The reason for using chicken liver juice is because it contains lots of purines, high levels of purines in the blood stimulate the production of uric acid through the enzyme xanthine oxidase (Kristiani *et al.*, 2013). At the same time, potassium oxonate is an inhibitor of the uricase enzyme which inhibits the activity of the uricase enzyme in the liver and produces excess uric acid in the blood of rat test animals. The uricase enzyme converts uric acid into allantoin whose function is easily excreted compared to uric acid. When the uricase enzyme is inhibited, uric acid levels increase (Dira and Harmely, 2014).

Matoa leaves contain secondary metabolite compounds such as containing secondary metabolite compounds of the flavonoid group, polyphenol tannins, alkaloids, and terpenoids which have very high pharmacological effects including antibacterial, antioxidant, and antifungal (Rossalinda *et al.*, 2021). The mechanism of action of flavonoids as anti-hyperuricemia compounds inhibits the activity of the xanthine oxidase enzyme in purine bases so that uric acid production will decrease (Harmanto, 2005; Ika *et al.*, 2017).

The test animals used in this study were white male rats. Test animals were divided into 5 groups with 5 animals per group. Group I Na CMC 1%, group II was given Allopurinol suspension 100 mg, group III, IV, and V were given a suspension of matoa leaf ethanol extract (EEDM) with dose variants of 200 mg/kg BW; 400 mg/kg BW; and 800 mg/kg BW. Before starting the test animal treatment, baseline uric acid (T0) levels were measured and then each group of test animals was induced with fresh chicken liver juice for 7 consecutive days. On day 8 induced potassium oxonate 250 mg/kg intraperitoneal body weight. The administration of EEDM drugs and therapy is carried out from the 8th to the 12th day. Measurement of uric acid levels was done on day 0 before treatment, 7, 8, and 12. From the results of measuring uric acid levels, uric acid levels were obtained in rat test animals, namely initial, induction, and therapy can be seen in **Table 1**.

Table 1. Results of measurement of uric acid levels in early, induction, and therapeutic rat test animals

Treatment Group	Average Measurement of Uric Acid Levels (mg/dL)		
	Early ± SD	Induction ± SD	Therapeutic ± SD
Group I Negative Control (Na-CMC)	3.80 ± 0.65	6.20 ± 2.33	5.26 ± 2.82
Group II Positive Control (Allopurinol 100 mg)	3.66 ± 0.83	6.10 ± 1.10	3.13 ± 1.85
Group III (EEDM 200 mg/kg BW)	3.60 ± 0.45	7.93 ± 2.32	6.00 ± 2.28
Group IV (EEDM 400 mg/kg BW)	3.80 ± 0.10	8.46 ± 1.36	6.03 ± 3.25
Group V (EEDM 800 mg/kg BW)	4.10 ± 0.173	9.10 ± 9.00	14.13 ± 5.75

From the measurement data obtained, quantitative data is made as Area Under Curve (AUC) in **Table 2**. Based on the results obtained from **Table 2** average AUC can be seen the largest AUC result is group V EEDM 800 mg/kg BW and the smallest positive control group is Allopurinol. The greater the AUC value, the smaller the effect of EEDM 800

mg/kg BW to reduce uric acid levels (Angkuna et al., 2019). This showed that ethanol extract of matoa leaves dose 200 mg/kg BW had almost the same anti-hyperuricemia effect as the positive control Allopurinol. Data from each treatment group were then statistically processed using the *Kruskal-Wallis* test. These observations show a significance value of 0.048 ($p < 0.05$), which means data distribution in a normally distributed sample. The analysis continued to the *Mann-Whitney follow-up* test to see differences between treatment groups.

Table 2. Average total AUC score of the treatment group

Treatment Group	AUC Value	Average
Negative Control (Na CMC)	5.8	5.73
	6.0	
	5.5	
Positive Control (Allopurinol)	4.7	4.61
	3.1	
	6.1	
EEDM 200 mg/kg BW	6.1	6.96
	8.7	
	6.1	
EEDM 400 mg/kg BW	7.1	7.25
	5.8	
	8.9	
EEDM 800 mg/kg BW	6.3	11.61
	8.8	
	19.8	

The results of the *Mann-Whitney* test showed that group I Na-CMC against group III (EEDM 200 mg/kg BW) and group V (EEDM 800 mg/kg BW) showed significantly different results with values ($p < 0.05$). This means that Na-CMC has no effect in reducing uric acid levels. In group II, Allopurinol's positive control of group Na-CMC and group IV (EEDM 400 mg/kg BW) showed results that did not differ markedly from the value ($p > 0.05$), this means that allopurinol, Na-CMC and group IV (EEDM 400 mg/kg BW) statistically had no effect in reducing urate asthma levels. Group III (EEDM 200 mg/kg BW) showed results that were not significantly different from group IV (EEDM 400 mg/kg BW) and group V (EEDM 800 mg/kg BW), but against group Na-CMC and allopurinol showed significantly different results with values ($p > 0.05$) this means that group III (EEDM 200 mg/kg BW), group IV (EEDM 400 mg/kg BW) and group V (EEDM 800 mg/kg BW) have the same effect in reducing uric acid levels.

Based on the results of research that has been conducted show that the dose of ethanol extract of matoa leaves that is effective in reducing uric acid levels is a dose of 200 mg/kg BW. It is suspected that matoa leaf ethanol extract contains flavonoid compounds that act as anti-hyperuricemia compounds by inhibiting the activity of xanthine oxidase enzyme in purine bases to reduce uric acid levels (Harmanto, 2005; Ika et al., 2017).

4. CONCLUSION

Based on the results of the anti-hyperuricemia effect test of matoa leaf in male rats, it can be concluded that EEDM has an anti-hyperuricemia effect on male rats with the most optimal dose in reducing uric acid levels is a dose of 200 mg/kg BW.

Acknowledgments: This work was supported by the Laboratory of Biopharmacy & Pharmacology, Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar.

Author Contribution: All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical Approval: -

REFERENCES

- Angkuna SA, Apridamayanti P, Sari R. Penentuan Waktu Optimum Produksi Bakteriosin dari *Lactobacillus casei* terhadap Bakteri Patogen *Staphylococcus aureus* dan *Escherichia coli*. 2019.
- Badulescu M, Macovei L, Rezus R. Acute Gout Sttack With Normal Serum Rric Acid Levels, The Medical-Surgical Journal. 2014.
- Dira & Harmely. Antihyperuricemia Activity Test of Sambilotto (*Androgravis paniculata* Nees), Brotowali (*Tinospora crispa* (L.) Hook & Thomson), Mangosteen (*Garcinia mangostana* L.), Black Pepper (*Piper nigrum* L.) and Ginger (*Zingiber officinale* Rosc.) In Vivo, Proceedings of the National Seminar and Workshop "Latest Development of Pharmaceutical and Clinical Science IV" Padang. 2014.
- Fawwaz M, Pratama M, Musafirah, Wahab I, Iriani R, Aminah, Kusuma AT, Arsul MI. Evaluation of Antioxidant Activity of *Vernonia*

- amygdalina* Leaves and Its Flavonoid-Phenolic Content. Indonesian Journal of Pharmaceutical Science and Technology. 2023; 10(2): 104-110.
- Hasyrul H, Sitti H, Widya R, Erlisa MP, Sylvan SP. Potensi Ekstrak Buah Matoa (*Pometia pinnata*) Sebagai Sumber Antioksidan. 2021.
- Harefa D. Utilization of Plant Products as Family Medicinal Plants (TOGA). Madani : Indonesia Journal of Civil Society. 2020.
- Harmanto N. Menggempur Asam Urat dan Rematik dengan Mahkota Dewa. 2005.
- Imbar C, Agista, Edwin DQ, Henki R. Uji Aktivitas Antihiperurisemia Ekstrak Etanol Tumbuhan Suruhan (*Peperomia pellucida* L.Kunth) Terhadap Tikus Putih Jantan (*Galur Wistar*) Yang Diinduksi Kafein. 2019.
- Ika DS, Dwi WE, Kusmiwiyati A. The effect of giving God's Crown boiled water (*Phaleria macrocarpa* (Scheff) Boerl) on blood uric acid levels in women, Journal of Health. 2017.
- Indrawan B, Kambayana G, Putra TR. The Relationship of High Purine Consumption with Hyperuricemia: A Cross-sectional Study in Balinese Tribes in Denpasar City, Journal of Internal Medicine Udayana. 2017.
- Kusuma UDP, Muslichah S, Ulfa EM. Test of Antihyperuricemia Activity of n-Hexane Extract, Ethyl Acetate, and 70% Ethanol Black Cumin Seeds (*Nigella sativa*) Against Hyperuricemia Mice, e journal Health Library. 2014.
- Lallo S, Mirwan M, Palino A, Nursamsinar, Hadrianti B. Activity of Red Ginger Extract in Reducing Uric Acid in Rabbits and Isolation and Identification of Bioactive Compounds, Indonesian Journal of Phytopharmaceuticals, 2018.
- Madoni A. The Effect of Warm Compresses Using Grated Ginger on Reducing the Intensity of Gout Arthritis Pain in the Elderly in the Working Area of Lubuk Begalung Health Center, Menara Ilmu. 2017.
- Kristiani RD, Rahayu D, Subarnas A. Antihyperuricemia Activity of Tangkus Fern Root Ethanol Extract (*Polypodium feei*) in Male Mice Journal of Life and Physical Sciences. 2013.
- Riskesdas. Riskesdas National Report. Ministry of Health of the Republic of Indonesia, Health Research and Development Agency, Jakarta. 2018.
- Riskesdas. South Sulawesi Provincial Report Riskesdas. Ministry of Health of the Republic of Indonesia, Health Research and Development Agency. Jakarta. 2018.
- Rossalinda, Wijayanti F, Iskandar D. Effectiveness of Matoa Leaf (*Pometia pinnata*) Extract as an Antibacterial *Staphylococcus epidermidis*. Stannum : Jurnal Sains dan Terapan Kimia. 2021.

This is an open access article which is publicly available on our journal's website under Institutional Repository at <https://www.umi.ac.id/id/>