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EFFECT OF MELINJO SEED EXTRACT ON URIC ACID LEVELS OF HYPERURICEMIC MALE WISTAR RATS

Al Ghiffari Muhammad Rayhan[1], Nani Maharani[2], Endang Mahati[2], Yora Nindita[2]*
[1]Undergraduate Program, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[2]Departement of Pharmacology and Therapy, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
*Corresponding Author : E-mail : nindita.yora@fk.undip.ac.id

ABSTRACK

Background : Uric acid is the end product of purine catabolism carried out in the liver. Increased level of uric acid in blood is called hyperuricemia, which might cause gout if it is not treated properly. Melinjo (*Gnetum gnemon L.*) plant is a native plant of Indonesia that contains flavonoids and stilbenoid potential as antihyperuricemia. **Aim :** This paper aimed to study the effect of melinjo seed extract on uric acid levels. **Methods :** Thirty-six male wistar rats were randomly divided into 6 groups, consists of healthy control group, hyperuricemic control, Allopurinol control, and treatment groups (3 groups). Hyperuricemia was induced by the administration of block broth and potassium oxonate for 4 weeks. Melinjo seed extract doses of 250, 500, and 2000 mg/kg BW, and allopurinol 90 mg/kg BW was given orally for 2 weeks. Statistical analysis was conducted to evaluate differences among groups before and after the intervention. **Results :** Three doses could significantly reduce uric acid levels ($p<0.05$) from 5.61±0.95 to 2.45±1.21; 5.86±1.84 to 2.04±1.11; and 5.95±0.91 to 3.59±1.58, respectively. However, there is no significant difference between the three doses. The effectiveness of melinjo seed extract at a dose of 500 mg/kg BW reduced uric acid levels by 65%, a dose of 250 mg/kg BW by 56%, and allopurinol 90 mg/kg BW by 10%. **Conlusion :** Melinjo seed extract can reduce uric acid levels even though there is no effect of graded dose.

Keywords : *Gnetum gnemon,, Hyperuricemia, Melinjo seeds, Uric Acid*

INTRODUCTION

People's lifestyles can contribute to the occurrence of health problems in Indonesia such as smoking habits, lack of activity, less nutritious drinks and food, and unhealthy environmental factors. This causes Indonesia to face not only a high number of infectious diseases, but also to face an increase in chronic degenerative diseases. Degenerative chronic diseases generally occur in the elderly. One of the most common health complaints among the elderly is the buildup of uric acid.[1]

Uric acid is the end product of purine mononucleotides catabolism into hypoxanthine and guanine which is carried out in the liver. In mammals other than primates, uric acid is further degraded by the uricase enzyme to allantoin, which is more water soluble than uric acid and can be efficiently excreted in the urine. This enzyme is not possessed by higher primates. Between 300 and 400 mg of purines are created and broken down every day. The kidneys normally expel roughly two-thirds of the body's uric acid load each day.[2] If uric acid is not metabolized and excreted properly, there will be an increase in blood uric acid levels, this is called hyperuricemia.[3]

Hyperuricemia occurs when uric acid levels exceed >7 mg/dl in men and >6 mg/dl in women.[4] Massive data on hyperuricemia in Indonesia is not yet known for certain, but several regions in Indonesia have conducted surveys on hyperuricemia data. In a study conducted in Depok, 18.6% of people experienced hyperuricemia and the prevalence of hyperuricemia in Denpasar City was 18.2%.[5] There are many factors thath influence hyperuricemia, these include the consumption of food high in purines and impaired excretion on the kidneys. Hyperuricemia that is not followed up will lead to deposits of uric acid crystals in the joint fluid called gout.[6,7]

Gout is an inflammation of the joints, bones, and soft tissues triggered by the release of lysosomal enzymes and the production of inflammatory chemokines by the activity of synovial phagocytic cells.[8] Based on the purpose of therapy, there are 2 groups of gout drugs. First, drugs that stop the acute inflammatory process such as colchicine, phenylbutazone, oxyfentabutazone, and indomethacin, and NSAIDs. The second is drugs that affect uric acid levels such as probenecid, sulfinpyrazone, and allopurinol.

Allopurinol competitively inhibits the enzyme xanthine oxidase, an important enzyme that plays a role in the uric acid synthesis, at low concentrations and is a noncompetitive inhibitor at

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high concentrations.[9] The disadvantage of drugs that affect uric acid levels, one of which is allopurinol, is that it can induce or increase the frequency of acute attacks at the beginning of therapy, therefore colchicine or NSAIDs are usually given in starting allopurinol treatment until serum uric acid levels decrease or are normal. Allopurinol also has side effects such as nausea, vomiting, skin rash, and other forms of hypersensitivity.[10,11]

Melinjo plant (*Gnetum gnemon L.*) is one of Indonesia's native plants that has many benefits. There has been many research developments on melinjo plants, regarding their leaf organs, skin, and seeds. Melinjo seeds contain flavonoid and stilbenoid compounds which include resveratrol, gnemonoside A, gnemonoside D, gnetin C, gnemonoside C, and gnetin L which are thought to has antioxidant, antibacterial, lipase, and amylase inhibitor.[12] Antioxidant compounds are believed to have the potential to inhibit the uric acid synthesis pathway as xanthine oxidase inhibitors.[13,14]

Based on these, a study was conducted using melinjo seed extract to reduce uric acid levels. Uric acid levels were assessed through rat blood serum and uric acid diagnostic reagents. The solution mixture is calculated for its absorbance wavelength using a spectrophotometer, then the absorbance results are entered for calculation using the formula for uric acid levels.

MATERIAL AND METHOD

This was a true experimental study with pre and post-test randomized controlled group design that was held from June to July 2022 in Universitas Diponegoro's Chemistry Laboratory, Animal Test Laboratory, and Intergrated Laboratory.

The tools used in this study includes rat drums and their accessories, experimental animal scales, sartorius scales, visible spectrophotometers and their equipment, gastric probes, disposable syringes, Erlenmeyer tubes for maceration, measuring cups, and water baths. The materials used include melinjo seeds obtained from farmers in the Gunung Sari area (Serang City, Indonesia) 70% ethanol solvent, 0.5% CMC (Sigma, St. Louis), aquades, Maggie® block broth, Potassium Oxonate (Solarbio, Beijing), Allopurinol (Omric, Medan), blood samples from male wistar rats, standard feed and experimental animal drinking water.

The samples used in this study were male wistar rats (*Ratuus norvegicus*) aged 8-12 weeks with the normal weight of 140-260 grams and in healthy physical condition, looked active, and had no anatomical abnormalities. The number of sample was 36 rats by WHO requirements and criteria.[15]

Thirty-six rats that fulfill the inclusion criteria were first adapted for 7 days in the laboratory by being given standard feed and drink, then the rats were randomly divided into 6 groups, each of which consisted of 6 rat samples. Group 0 (K0) as the healthy control was only given standard feed. Group 1 (K1) as the negative control was only hyperuricemia induced. Group 2 (K2) as the positive control was given allopurinol orally at a dose of 90 mg/kgBW rats. Treatment 1 (P1), Treatment 2 (P2) and Treatment 3 (P3) as treatment groups were given melinjo seed extract orally at a dose of 250 mg/kgBW, 500 mg/kgBW, and 2000 mg/kgBW.

The treatment was carried out for 28 days by providing high-purine feed as an induction of hyperuricemia and still being given standard feed and drink. On day 21 of the study, blood samples were taken through the retro orbital plexus to determine the blood uric acid levels of the rats before giving the intervention with the aim of knowing that the rats were hyperuricemic. On day 22, intervention was carried out according to the treatment groups for 14 days. On Day 35, blood samples were taken from the retro orbital plexus to determine post-intervention uric acid levels; however, one hour before blood sampling, 250 mg/kgBW of potassium oxonate was injected intraperitoneally.

The respective data were then analysed using IBM SPSS Statistics 26.0 Software. Data was analyzed using paired T-test and Wilcoxon, as well as Kruskall Wallis test, followed by Mann Whitney test as a Post Hoc test.

RESULTS

This study used melinjo seeds (*Gnetum gnemon L.*) obtained from farmers around Gunung Sari, Serang. Melinjo seeds were separated from the skin and then crushed into gravel size and dried to reduce the water composition so that withdrawal of active substance by the solvent before extraction is better. Simplicia was soaked in 70% ethanol for 12-

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24 hours then filtered before evaporation. Evaporation was done over a water bath until a thick extract consistency was formed. From this process, 63.55 grams of melinjo seed extract was obtained.

The research sample consisted of 36 male wistar rats obtained from Farmouse Ungaran, Semarang, Central Java. The samples were divided into 6 groups with each group consisting of 6 rats. Before the treatment, rats were acclimatized for 7 days and given standard feed. During the treatment period, there were 4 rats that dropped out or did not meet the inclusion criteria in each group, K1, P1, P2, and P3, due to death and physical defects, so the number of samples that met the inclusion criteria was 32 rats.

Measurement of uric acid levels before and after treatment (Day 21 and 35) obtained data on the average uric acid levels before and after treatment as stated in table 1.

Table 1. Uric acid levels before and after treatment

Groups	N	Before		After		Before and After Comparison
		(Mean ± SD)	$p^{£}$	(Mean ± SD)	$p^{£}$	*p*
K0	6	2.93 ± 0.82	0.124	1.55 ± 0.66	0.120	0.037*
K1	5	6.56 ± 1.43	0.424	6.75 ± 3.16	0.008	0.686**
K2	6	5.39 ± 1.59	0.005	5.31 ± 2.20	0.348	0.917**
P1	5	5.61 ± 0.95	0.125	2.45 ± 1.21	0.060	0.003*
P2	5	5.86 ± 1.84	0.737	2.04 ± 1.11	0.160	0.012*
P3	5	5.95 ± 0.91	0.250	3.59 ± 1.58	0.125	0.01*

£Saphiro-Wilk (significant p>0.05); *Paired T-Test (significant p<0.05); **Wilcoxon Test (significant p<0.05)

Uric acid levels before and after treatment are presented in Table 1. Serum uric acid levels before treatment were >5 mg/dl in groups K1, K2, P1, P2, and P3 in which the study succeeded in inducing hyperuricemia in rats.[16] The smallest average uric acid level after treatment was at K0, while the highest average uric acid level was at K1.

Analysis of data normality using the Shapiro-Wilk test showed that the data were not normally distributed in the K2 group before treatment and in the K1 group after the treatment. Based on this, to analyze the difference in the results of uric acid levels between before and after treatment in each group, paired T-test was used in the normally distributed data group and Wilcoxon test was used in the abnormal data groups, namely the K1 and K2 groups.

Comparisons of uric acid levels before and after treatment are presented in Table 2. These were analyzed with the Paired T-test in groups K0, P1, P2, and P3, as well as the Wilcoxon test in groups K1 and K2. There were significant difference in groups K0, P1, P2, and P3 ($p < 0.05$). Based on these, it can be seen that in groups K0, P1, P2, and P3 there was a change with a significant decrease in uric acid levels after treatment.

Table 2. Comparison of decreased uric acid levels (after treatment) between groups

Grou	*P* Value after Treatment				
p	K1	K2	P1	P2	P3
K0	0,044*	0,004*	0,099	0,462	0,054
K1	-	0,233	0,116	0,117	0,117
K2		-	0,028*	0,028*	0,272
P1			-	0,293	0,207
P2				-	0,142

*Significant (p<0,05)

The result Kruskal Wallis test was a significant difference in the results of uric acid levels before treatment between groups and in the results of uric acid levels after treatment (p<0,05). A post hoc test using the Mann-Whitney on uric acid level data after treatment to determine the level of statistical significance of each group.

The results of the Mann-Whitney test are presented on Table 2. There were significant differences in the K0 group against K1 and K2. The next significant difference was found in Group K2 against P1 and P2. There were no significant difference between treatment groups P1, P2, and P3 which means that there was no effect of graded dose

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between 250 mg/kgBB, 500 mg/kgBB, and 2000 mg/kgBW of melinjo seed extract on uric acid levels in this study.

DISCUSSION

In this study, researchers succeeded in inducing hyperuricemia in groups including K1, K2, P1, P2, and P3 with an average uric acid level of 5.8 mg/dl. Maggie® block broth as an induction agent contains monosodium glutamate (MSG), disodium inosinate, guanylate, and yeast extract. Disodium inosinate and guanylate are purine nucleotides.[17] Excessive intake of purine nucleotides can increase blood uric acid levels.[18] Potassium oxonate is an uricase selective competitive inhibitor which blocks the action of the enzyme uricase in the liver, causing hyperuricemia in rodents. Besides in rats, the use of potassium oxonate at a dose of 80 mg/kgBW was able to induce hyperuricemia in squirrels (*Tupaia belangeri chinensis*).[19]

A significant decrease in uric acid levels occurred after administration of melinjo seed extract (250 mg/kgBW, 500 mg/kgBW, 2000 mg/kgBW) proves that the bioactive compounds in melinjo seeds affect the activity of uric acid synthesis in the blood. This process occurs through an inhibitor of the xanthine oxidase enzyme which produces free radicals in the form of hydrogen peroxide and superoxide anion.[16] Melinjo seeds contain antioxidant compounds in the form of flavonoids and stilbenoids which include gnemonoside A, gnemonoside D, gnetin C, gnemonoside C, and gnetin L, as well as resveratrol.[20] Based on the comparison of the antioxidant activity test, the ethanol fraction of melinjo seeds was slightly better than that of melinjo seeds, this is supported by the value of the flavonoid content of melinjo seeds being greater than that of melinjo skin, namely 172.57 ± 18.01 mg QE/g of melinjo seed extract and 145.00 ± 23.79 mg QE/g melinjo peel extract.[14] In vitro, hydrophobic interactions between flavonoids and the enzyme xanthine oxidase play an important role in inhibiting the activity of the xanthine oxidase enzyme. The planar structure and C2=C3 double bonds of flavonoids are beneficial for binding and inhibiting xanthine oxidase activity.[21]

A significant comparison of uric acid levels after treatment was found in the K2 group and the P1 and P2 groups. Melinjo seed extract 500 mg/kgBW had the largest percentage in reducing uric acid levels, namely 65%, then 56% in the P1 group which were given 250 mg/kgBW melinjo seed extract, and 10% allopurinol 90 mg/kgBW. This is similar to a study by Puspita (2018) which showed that administering allopurinol 90 mg/kgBW for 4 weeks had an effectiveness in reducing serum uric acid levels in mice, which was lower at 42.02%, while melinjo peel extract 900 mg/kgBW showed a percentage of 54.65%.[16]

In this study, allopurinol can reduce uric acid levels but not significantly. This is not in line with Addinurrahmat's research (2017) which shows that there was a significant decrease in uric acid levels ($p < 0.001$) in the administration of allopurinol at a dose of 90 mg/kgBW in wistar rats for 12 days from 8.07 mg/dl to 3.03 mg/dl.[22] Administration of a combination of allopurinol and probenecid was reported to be more effective in reducing uric acid, than the group that was only given allopurinol and probenecid monotherapy in hyperuricemic rabbit samples.[23]

Comparison between treatment groups (P1, P2, P3) did not show significant results; thus, there was no relationship between stratified dose effects. The relationship between drug dose and the effect produced in the clinic is usually quite complex and influenced by many factors. The response to an effect usually increases in proportion to the high dose of drug administered, but as the dose of the drug increases, the increase in response decreases and eventually reaches a dose at which the response can no longer be increased. If the dose is increased again, there will be toxic to lethal effects. This may happen in this study, in which giving melinjo seed extract at a dose of 2000 mg/kgBW is not better than 500 mg/kgBW.[11,24]

It is commonly assumed that excessive consumption of melinjo seeds can cause complications of various health problems, this is contrary to the potential of the melinjo seeds. In a study by Tani *et al* (2014) research subjects were monitored regarding their body weight, blood pressure, and pulse rate while consuming melinjo seed extract for 28 days with doses of 1000, 2000, and 5000 mg, no changes were found, indicating that giving melinjo seeds up to a dose of 5000 mg per day in humans is safe, at least in the short term such as 1 month with reasonable consumption.[25]

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The limitations of this study were that no quantitative phytochemical tests were carried out so that levels of stilbenoids and flavonoids in the samples of melinjo seed extract cannot be detects.

CONCLUSION

Melinjo seed extract (*Gnetum gnemon L.*) can reduce uric acid levels, in which the effective dose is 500 mg/kgBW with the effectiveness of reducing uric acid levels by 65%. there is no dose effect relationship from the effect of giving melinjo seed extract in three graded doses in this study.

ETHICAL APPROVAL

This research has received ethical permission from the KEPK (Commission on Ethics for Medical and Health Research) Faculty of Medicine, Diponegoro University with No.48/EC/H/FK-UNDIP/VI/2022.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Pusdatin Kemenkes RI. Gambaran Kesehatan Lanjut Usia di Indonesia. In: Pusat Data dan Informasi Kementerian Kesehatan RI. 1st ed. Jakarta: Kementerian Kesehatan Republik Indonesia; 2013. p. 1–5.
2. Chaudhary K, Malhotra K, Sowers J, Aroor A, Annayya Aroor A. Uric Acid-Key Ingredient in the Recipe for Cardiorenal Metabolic Syndrome Chaudhary et al.: Uric Acid-Key Ingredient in the Recipe for Cardiorenal Metabolic Syndrome. Cardiorenal Med. 2013;3:208–20. doi : 10.1159/000355405
3. Park JH, Jo Y Il, Lee JH. Renal effects of uric acid: Hyperuricemia and hypouricemia. Korean J Intern Med. 2020;35(6):1291–304. doi : 10.3904/kjim.2020.410
4. Jin M, Yang F, Yang I, Yin Y, Luo JJ, Wang H, et al. Uric acid, hyperuricemia and vascular diseases. Front Biosci. 2012;17(2):656–69. doi : 10.2741/3950/PDF
5. Indrawan IB, Kambayana G, Putra TR. Hubungan Konsumsi Purin Tinggi Dengan Hiperurisemia: Suatu Penelitian Potong Lintang Pada Penduduk Suku Bali di Kota Denpasar. J Penyakit Dalam Udayana. 2017;1(2):38–44.
6. Uy BD. Hyperuricemia. In: Ferri FD, editor. Ferri's Clinical Advisor 2022. 1st ed. Philadelphia: Elsevier; 2021. p. 97–8.
7. Putra TR. Hiperurisemia. In: Setiati S, editor. Buku Ajar Ilmu Penyakit Dalam Jilid 3 Edisi 6. 6th ed. Jakarta: Interna Publishing; 2014. p. 3181–6.
8. Narang RK, Dalbeth N. Pathophysiology of Gout. Semin Nephrol. 2020;40(6):550–63. doi : 10.1016/j.semnephrol.2020.12.001
9. Brunton LL, Knollmann BC, Hilal-Dandan R. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. Brunton LL, editor. New York: McGraw-Hill Education; 2018. 702 p.
10. Gan S, Wilmana PF. Analgesik-Antipiretik Analgesik Anti-Inflamasi Non-Steroid dan Obat Gangguan Sendi laiinya. In: Gan S, editor. Farmkologi dan Terapi. 6th ed. Jakarta: Badan Penerbit FKUI; 2016. p. 234–51.
11. Katzung BG, Masters SB, Trevor AJ. Farmakologi Dasar & Klinik Edisi 12. 12th ed. Katzung BG, editor. New York: The McGraw-Hill; 2013. 653–654 p.
12. Tatefuji T, Yanagihara M, Fukushima S, Hashimoto K. Safety assessment of melinjo (*Gnetum gnemon L.*) seed extract: Acute and subchronic toxicity studies. Food Chem Toxicol. 2014;67:230–5. doi : 10.1016/j.fct.2014.02.030
13. Wulandari S, Subandi, Muntholib. Inhibisi Xantin Oksidase oleh Ekstrak Etanol Kulit Melinjo (*Gnetum gnemon*) Relatif terhadap Allopurinol. J Online Univ Negeri Malang. 2012;1(1):1–9.
14. Rosa D, Yuswandi MA, Siregar TM, Sugata M, Arianditha E. Uji Aktivitas Antioksidan Ekestrak Biji dan Kulit Buah Melinjo. FaST-J Sains dan Teknol. 2020;4(1):92–8.
15. WHO. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine World Health Organization.

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JKD (DMJ), Volume 12, Number 1, January 2023 : 10-15

Geneva: WHO; 2000. 1–73 p.
16. Ayu Puspita C. Efektivitas Ekstrak Kulit Melinjo (*Gnetum gnemon*) sebagai Penurun Kadar Asam Urat pada Tikus Putih (*Rattus norvegicus*). [Thesis]. Institut Pertanian Bogor; 2018.
17. Burdock GA. Fenaroli's Handbook of Flavor Ingredients. In: Fenaroli's Handbook of Flavor Ingredients. 6th ed. Fl: CRC Press; 2010. p. 2162.
18. Murray RK, Granner DK, Mayes PA, Rodwell VW. Harper's Illustrated Biochemistry. 27th ed. Vol. 27, British Medical Bulletin. New York: Lange Medical Books/Mc Graw-Hill; 2006. 703 p.
19. Tang DH, Ye YS, Wang CY, Li ZL, Zheng H, Ma KL. Potassium oxonate induces acute hyperuricemia in the tree shrew (*Tupaia belangeri chinensis*). Exp Anim. 2017;66(3):209–16.
20. Kato E, Tokunaga Y, Sakan F. Stilbenoids isolated from the seeds of Melinjo (*Gnetum gnemon L.*) and their biological activity. J Agric Food Chem. 2009;57(6):2544–9. doi : 10.1021/JF803077P
21. Huang J, Wang S, Zhu M, Chen J, Zhu X. Effects of genistein, apigenin, quercetin, rutin and astilbin on serum uric acid levels and xanthine oxidase activities in normal and hyperuricemic mice. Food Chem Toxicol. 2011;49(9):1943–7. doi : 10.1016/j.fct.2011.04.029
22. Addinurrahmat D. Pengaruh Infusa Daun Jeruju (*Acanthus ilicifolius*) Terhadap Kadar Asam Urat Darah Tikus (*Rattus novergicus*) Hiperurisemia [Thesis]. Universitas Brawijaya; 2017.
23. Fardin, Onsi R. Pengaruh Pemberian Alopurinol Tablet dan Probenesid Tablet terhadap Kadar Asam Urat Darah Kelinci yang Diinduksi Kalium Oksonat. Maj Farm Nas. 2019;16(1):49–55.
24. Setiawati A, Suyatna FD, Gayatri A. Pengantar Farmakologi. In: Gunawan SG, editor. Farmkologi dan Terapi. 6th ed. Jakarta: Badan Penerbit FKUI; 2016. p. 1–28.
25. Tani H, Hikami S, Iizuna S, Yoshimatsu M, Asama T, Ota H, et al. Pharmacokinetics and safety of resveratrol derivatives in humans after oral administration of melinjo (*Gnetum gnemon L.*) seed extract powder. J Agric Food Chem. 2014;62(8):1999–2007. doi : 10.1021/jf4048435