**Volume 4, Nomor 3, September 2023** **ISSN : 2774-5848 (Online)**
**ISSN : 2774-0524 (Cetak)**

# *ETHANOLIC EXTRACT SIRIH CHINA (Peperomia Pellucida) ON REDUCING URIC ACID LEVELS IN WISTAR RATS MODEL HYPERURICEMIA WITH HIGH FRUCTOSE INDUCED*

**Armansyah Maulana Hrahap[1*]**
Faculty of Pharmacy Universitas Indonesia, Depok 16424, West Java, INDONESIA[1]
**Corresponding Author* : armansyah.maulana@ui.ac.id

## ABSTRAK
Daun Sirih China merupakan tanaman yang banyak tumbuh di daerah lembab dengan persebaran yang banyak sehingga jarang digunakan dengan kebutuhan yang jelas dan komersial, namun secara empiris sudah banyak digunakan sebagai obat tradisional yang dipercaya berperan penting dalam menurunkan kadar asam urat akan tetapi masih belum banyak penelitian yang menemukan dosis penggunaan yang tepat. Oleh karena itu, penelitian ini bertujuan untuk mengetahui efek antihiperurisemik daun sirih cina (*Perperomia pellucida*) dan penggunaan dosis yang tepat pada tikus Wistar yang diinduksi hiperurisemia akibat fruktosa tinggi. Penelitian ini menggunakan desain penelitian eksperimental murni, menggunakan desain kelompok kontrol *pretest-posttest*, untuk mengevaluasi efek antihiperurisemik ekstrak daun sirih China. Hewan percobaan dibagi menjadi 6 kelompok (Kontrol, CMC, Allopurinol dan kelompok variasi dosis 250, 350 dan 500 mg / KgBB, pengukuran kadar asam urat dilakukan pada minggu ke 0, 6, 9, 12 dan 15. Penelitian ini menyelidiki efek antihiperurisemik ekstrak etanol daun sirih Cina Perperomia pelusida pada tikus Wistar yang diinduksi hiperurisemia. Menggunakan desain kelompok kontrol pretest-posttest, penelitian ini menemukan bahwa ekstrak tersebut secara signifikan mengurangi kadar asam urat, terutama pada dosis 350 mgKgBB. Temuan ini menunjukkan aplikasi terapeutik potensial dari ekstrak daun sirih Cina dalam mengelola hiperurisemia (P<0,05).

**Kata kunci** **:** hiperurikemia, fruktosa, sirih Cina, *peperomia pellucida*

## *ABSTRACT*
*Chinese betel leaf is a plant that grows in humid areas with a wide distribution so it is rarely used with clear and commercial needs, but empirically it has been widely used as a traditional medicine that is believed to play an important role in lowering uric acid levels but there are still not many studies that find the right dose of use. Therefore, this study aims to determine the antihyperuricemic effect of Chinese betel leaf (Perperomia pellucida) and the use of appropriate doses in Wistar rats induced hyperuricemia due to high fructose. This study used a purely experimental study design, using a pretest-posttest control group design, to evaluate the antihyperuricemic effect of Chinese betel leaf extract. The experimental animals were divided into 6 groups (control, CMC, Allopurinol and dose variation groups of 250, 350 and 500 mg / KgBB), uric acid levels were measured at Weeks 0, 6, 9, 12 and 15. This study investigated the antihyperuricemic effect of ethanol extract of Chinese betel leaf Perperomia pellucida on hyperuricemia-induced Wistar rats. Using a pretest-posttest control group design, the study found that the extract significantly reduced uric acid levels, especially at doses of 350 mgKgBB. These findings suggest a potential therapeutic application of Chinese betel leaf extract in managing hyperuricemia (P<0.05)..*

***Keywords*** ***:*** *hyperuricemia, fructose, chinese betel, peperomia pelllucida*

## INTRODUCTION

Hyperuricemia is an abnormal condition that occurs in the body's metabolism caused by high consumption of purines and the presence of several processes that cause uric acid levels in the body to increase and have an impact on high nucleic acid metabolism in the body which is controlled by Xanthine oxidase enzyme activity so that it is from the normal threshold. namely 7 mg/dL for men and 6 mg/dL for women(Benn et al., 2018; Kushiyama et

al., 2016; Yamanaka, 2012). Improper handling of hyperuricemia can cause many complications such as the accumulation of crystals at a certain point which triggers calcification and even has the potential to cause inflammation and lead to rheumatoid arthritis, which is a joint disorder characterized by the formation of tophi and the possibility of damage or injury. on the kidneys(Moser et al., 2015; et al., 2020).

Pillars of handling cases of hyperuricemia are carried out by implementing several management treatments as follows: Providing education, physical activity such as regular exercise, regulating diet, especially purines and finally providing pharmacological intervention of herbal medicines. Pillars that are being studied in depth are directed to pharmacological treatment using herbs as treatment interventions with the hope that herbs can suppress the work of purine metabolism so that they can act as inhibitors for molecules related to purine metabolism and it is also hoped that the application of herbal pillars can eliminate side effects from drug use. -Generic drugs/chemicals in the market that are already in circulation(Koto et al., 2020; Li et al., 2019).

The prevalence of hyperuricemia from time to time has developed and increased throughout the world. The Global Burden of Diseases (GBD) released data and showed that the prevalence of hyperuricemia for the Indonesian region was in the range of 15%-18%[8]. However, the data for the prevalence of hyperuricemia in Indonesia still do not have definitive data for the whole, this is because Indonesia has a large area so that it is possible to have varied data. However, research using epidemiology on the prevalence of hyperuricemia was carried out by[9] in the Central Java region and then obtained a prevalence result of 28% where men had a much different percentage from women, which was 21% while women had 7%. There are several factors that can cause differences in the percentage of uric acid for certain areas such as gender, age, hypertension, insulin resistance, obesity and can also be caused by exogenous purine levels obtained from daily food sources(Cheng-yuan & Jian-gang, 2023; Sharma et al., 2021).

Scientifically various ways have been done to control cases of hyperuricemia before it manifests into other more severe diseases, including controlling uric acid production by increasing the expression of transporter proteins that play a role in removing urine from the body through urination, and or can also be done by slowing and inhibiting processes. The formation of uric acid in the body is controlled by the enzyme guanase and the enzyme xanthine oxidase. Allopurinol is one of the generic production drugs which is an XDH Inhibitor which functions to weaken the working system of the xanthine oxidase enzyme so that it weakens the production of uric acid in the body and has an impact on reducing uric acid levels in the body's plasma(Han et al., 2020; Machrina et al., 2018; Pavelcova et al., 2020). The use of Allopurinol turns out to still have mild effects and lead to fatal if not with the right use and application methods, such as the occurrence of allergic effects on a mild to severe scale, having toxic effects on the kidneys and liver which can be characterized by inflammation and inflammation in both(Anugerah & Rahman, 2023). Pharmacologically Allopurinol itself has a high interaction with other drugs such as warfarin and cyclorscopy(Harahap & Machrina, 2022). Studies that have been done have shown that the interaction between allopurinol and warfarin can reduce the efficacy of the liver, thereby reducing the work of the liver in metabolizing the drug, while the interaction between allopurinol and cyclorscopy causes an increase in plasma cyclorscopy(Chen et al., 2016).

*Peperomia pellucida* has colloquial terms as Chinese betel, suruhan and ketumpang water which has many benefits and is used empirically by the community as an antihyperuricemic drug, traditionally used in tea brewing models. Based on a research study conducted by stated that Chinese betel has a lot of flavonoid compounds and functions as an inhibitor of the activity of the xanthine oxidase enzyme. Further research conducted by explained that the effect of giving Chinese betel extract to caffeine-induced hyperuricemia

model Wistar rats had the effect of reducing uric acid levels at a dose of 400 mg/KgBW(Adhityasmara et al., 2020; Hasan et al., 2020; Iaccarino et al., 2021). Therefore, this study aims to determine the antihyperuricemic effect of Chinese betel leaf (Perperomia pellucida) and the use of appropriate doses in Wistar rats induced hyperuricemia due to high fructose

## METHOD

Type of experimental study with pre-post-test design in animals try to model high fructose induced hyperuricemia. The study was conducted in the Laboratory of Biology, Animal Housing Unit, Universitas Negeri Medan for 15 days of observation, with the observation parameters of uric acid levels taken by dislocation at the tail end of the experimental animal with the provisions of >2 mg/dL included in the criteria of uric acid. Statistical analysis was conducted using dependent t-tests or the Mann-Whitney test, depending on data distribution.

## RESULTS

The results of the measurement of the average uric acid level of all groups of rats/tested animals were carried out for 14 days of observation starting from day 0 of the study. The results can be seen in Table 1 as follows:

**Table 1. The results of the average measurement of uric acid levels before and after the induction of high fructose.**

| Dose (mg/KgBW) | Before induce (mg/dL) | After induce (mg/dL) | | | |
|---|---|---|---|---|---|
| | Day 0 | Day 6 | Day 9 | Day 12 | Day 15 |
| Control | 2.1 | 1.8 | 2.2 | 5.5 | 2.3 |
| CMC | 1.3 | 3.1 | 5.9 | 6.2 | 16.7 |
| Allopurinol | 1.9 | 2.4 | 3.9 | 9.7 | 13.2 |
| Dose 250 | 2.9 | 2.8 | 3.6 | 8.8 | 11.4 |
| Dose 350 | 4.3 | 7.5 | 9.6 | 10.4 | 12.7 |
| Dose 500 | 3.5 | 5.8 | 3.3 | 9.7 | 12.4 |

The graph below is a graph showing the increase in uric acid levels after fructose induction with evaluation of observations for 15 days compared to the six groups, namely control, CMC, Allopurinol doses of 250 mg/KgBW, 350 mg/KgBW and 500 mg/KgBW as follows:

Then based on Table 2, it can be seen the levels in the percentage of uric acid reduction after giving the intervention of ethanol extract of betel leaf china for 1 month of extract intervention.

**Table 2. Percentage of decrease in uric acid levels after the intervention of China betel leaf ethanol extract**

| Groups | Dose (mg/kgbw) | Day-9 | Day-12 | Day-15 |
|---|---|---|---|---|
| control | - | | | |
| CMC | 0.5% | | | |
| Alopurinol | 10 | 47.05 % | 36.63 % | 56.68 % |
| EESC | 250 | 44.44 % | 40.43 % | 46.29 % |
| EESC | 350 | 51.59 % | 53.98 % | 63.56 % |
| EESC | 500 | 43.53 % | 53.06 % | 58.84 % |

Table 2 describes a decrease in uric acid levels in the blood higher on Day 15 at a dose of 300 mg / KgBW with a percentage of 63.5 %

**Table 3. After Intervention of Etanolic Extract Sirih China**

| **Dose** | After Intervention of Etanolic Extract Sirih China | | | | |
|---|---|---|---|---|---|
| | **week 0** | **week 1** | **Week 2** | **Week 3** | **Week 4** |
| Normal | 2.3 | 3.8 | 2.2 | 2.5 | 4.2 |
| CMC | 16.7 | 13.1 | 16.9 | 16.2 | 16.7 |
| Allopurinol | 13.2 | 12.4 | 9.9 | 9.7 | 8.2 |
| Dose 250 | 11.4 | 12.8 | 9.6 | 8.8 | 8.4 |
| Dose 350 | 12.7 | 7.5 | 6.6 | 6.4 | 5.7 |
| Dose 500 | 12.4 | 13.8 | 11.3 | 9.7 | 7.4 |

Table 3 describes the reduction in uric acid levels in the group given ethanol extract treatment betel china, the third dose showed a decrease, but the group with a dose of 300 mg / KgBW showed a significant decrease compared to other doses.

**Table 4. Average Decrease in Uric Acid Levels**

| **Dose** | **Serum Uric Acid Mean ±SD** | **p Value** |
|---|---|---|
| Dose 250 | 8,1 ± 2,3 | 0,087 |
| Dose 350 | 8,1 ± 3,4 | 0,032 |
| Dose 500 | 5,7 ± 2,8 | 0,001 |

Values measured in the group with ethanol extract measurement of Chinese betel with dose measurement of 300 mg/KgBW and 500mg / KgBW with P values respectively (p= 0.032 and p=0.001).

## DISCUSSION

Regulation and gene expression of XDH, further analysis was used based on observations of regulation and expression of the XDH gene to see how important the XDH role was in responding to substances that cause uric acid formation, it was found that Xdh gene expression increased along with the mechanism is to carry out the oxidation of purine product changes from exposure to substances that cause hyperuricemia. Conducted a similar study with different herbs, namely the Ganghwuhaljetengyoum plant extract which is an herbal plant that was designed with several doses used to rats and evaluated uric acid levels and examination of XDH gene expression. Obtained a decrease in XDH expression after administration. Ganghwuhaljetengy oum plant extract, so that the potency of plants affects the regulation of XDH which plays an important role in the formation of purines in the body. The results of this study are in accordance with previous research that proves allopurinol works as an inhibitor of XDH can reduce uric acid levels. The mechanism of action of allopurinol is not in accordance with the treatment in rats Wistar model of hyperuricemia and given high fructose, so the dose of allopurinol at a dose of 10 mg/KgBB has no effect in reducing the work of XDH(Zell & Carmichael, 1989).

(Oh et al., 2019) conducted a similar study with different herbs, namely Ganghwuhaljetengyoum plant extract which is a herbal plant that is desaign with several doses used to mice and carried out evaluation of uric acid levels and examination of XDH gene expression, a decrease in expression of XDH was obtained after administration of Ganghwuhaljetengyoum plant extract, so that the potential of plants affects a lot from XDH regulation which plays an important role in the formation of purines in the body. (Huff et al., 2017) gene regulation and expression of XDH, a follow-up analysis was used based on the

observation of regulation and expression of the XDH gene to see how the important role of Xdh in responding to substances that cause uric acid formation, it was obtained that XDH gene expression increases along with its mechanism to oxidize changes in purine products from exposure to substances that cause hyperuricemia.

## CONCLUSION

A dose of 350 mg/KgBW showed a significant decrease in uric acid levels on the 15th day of study observation

## ACKNOWLEDGMENTS

I would like to thank all parties who supported and helped in this research process, especially to Animal laboratory of Universitas Negeri Medan.

## REFERENCE

Adhityasmara, D., Dian Advistasari, Y., & Nugraheni, B. (2020). Aktivitas Antihiperurisemia Mikroenkapsulasi Ekstrak Kulit Melinjo (Gnetum gnemon L.) secara In Vivo. *Parapemikir : Jurnal Ilmiah Farmasi*, *9*(1), 1–6. https://doi.org/10.30591/pjif.v9i1.1843

Anugerah, P., & Rahman, S. (2023). The Effect of Binahong (Anredera cordifolia (Ten.) Steenis) Leaf Ethanolic Extract on the Reduction of Blood Uric Acid Levels in Hyperuricemic Male White Wistar Rats (Rattus norvegicus). *Folia Medica Indonesiana*, *59*(1), 20–25. https://doi.org/10.20473/fmi.v59i1.36052

Benn, C. L., Dua, P., Gurrell, R., Loudon, P., Pike, A., Ian Storer, R., & Vangjeli, C. (2018). Physiology of hyperuricemia and urate-lowering treatments. *Frontiers in Medicine*, *5*(MAY), 1–28. https://doi.org/10.3389/fmed.2018.00160

Chen, C. J., Lü, J. M., & Yao, Q. (2016). Hyperuricemia-related diseases and xanthine oxidoreductase (XOR) inhibitors: An overview. *Medical Science Monitor*, *22*, 2501–2512. https://doi.org/10.12659/MSM.899852

Cheng-yuan, W., & Jian-gang, D. (2023). Research progress on the prevention and treatment of hyperuricemia by medicinal and edible plants and its bioactive components. *Frontiers in Nutrition*, *10*(June), 1–14. https://doi.org/10.3389/fnut.2023.1186161

Han, S., Wei, R., Han, D., Zhu, J., Luo, W., Ao, W., & Zhong, G. (2020). Hypouricemic Effects of Extracts from Urtica hyperborea Jacq. ex Wedd. In Hyperuricemia Mice through XOD, URAT1, and OAT1. *BioMed Research International*, *2020*. https://doi.org/10.1155/2020/2968135

Harahap, A. M., & Machrina, Y. (2022). *EFFECT OF PHYSICAL ACTIVITY Fast Interval Training AND PROVISION OF SKIN MELINJO EXTRACT (Gnetum gnemon) ON EXPRESSION URAT1, GLUT9 AND SGLT2 IN HYPERURICEMIA INSULIN RESISTANCE*. *8*(1), 14–23. https://doi.org/10.24114/jbio.v8i1.29105

Hasan, A. E. Z., Puspita, C. A., & Setiyono, A. (2020). Efektivitas Ekstrak Kulit Melinjo (Gnetum gnemon) sebagai Penurun Kadar Asam Urat pada Tikus Putih (Rattus norvegicus) Hiperurisemia. *Curr. Biochem*, *7*(1), 21–28.

Huff, R. D., Hsu, A. C. Y., Nichol, K. S., Jones, B., Knight, D. A., Wark, P. A. B., Hansbro, P. M., & Hirota, J. A. (2017). Regulation of xanthine dehydrogensase gene expression and uric acid production in human airway epithelial cells. *PLoS ONE*, *12*(9), 1–17. https://doi.org/10.1371/journal.pone.0184260

Iaccarino, G., Franco, D., Sorriento, D., Strisciuglio, T., Barbato, E., & Morisco, C. (2021). Modulation of Insulin Sensitivity by Exercise Training: Implications for Cardiovascular

Prevention. *Journal of Cardiovascular Translational Research*, *14*(2), 256–270. https://doi.org/10.1007/s12265-020-10057-w

Koto, R., Nakajima, A., Horiuchi, H., & Yamanaka, H. (2020). Real-world treatment of gout and asymptomatic hyperuricemia: A cross-sectional study of Japanese health insurance claims data. *Modern Rheumatology*, *31*(1), 261–269. https://doi.org/10.1080/14397595.2020.1784556

Kushiyama, A., Nakatsu, Y., Matsunaga, Y., Yamamotoya, T., Mori, K., Ueda, K., Inoue, Y., Sakoda, H., Fujishiro, M., Ono, H., & Asano, T. (2016). Role of uric acid metabolism-related inflammation in the pathogenesis of metabolic syndrome components such as atherosclerosis and nonalcoholic steatohepatitis. *Mediators of Inflammation*, *2016*. https://doi.org/10.1155/2016/8603164

Li, Q., Li, X., Wang, J., Liu, H., Kwong, J. S. W., Chen, H., Li, L., Chung, S. C., Shah, A., Chen, Y., An, Z., Sun, X., Hemingway, H., Tian, H., & Li, S. (2019). Diagnosis and treatment for hyperuricemia and gout: A systematic review of clinical practice guidelines and consensus statements. *BMJ Open*, *9*(8), 1–13. https://doi.org/10.1136/bmjopen-2018-026677

Machrina, Y., Al-Rasyid Damanik, H., Purba, A., & Lindarto, D. (2018). Effect various type of exercise to Insr gene expression, skeletal muscle insulin receptor and insulin Resistance on Diabetes Mellitus Type-2 model Rats. *International Journal of Health Sciences*, *6*(4), 2372–5079. https://doi.org/10.15640/ijhs.v6n4a8

Moser, O., Tschakert, G., Mueller, A., Groeschl, W., Pieber, T. R., Obermayer-Pietsch, B., Koehler, G., & Hofmann, P. (2015). Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. *PLoS ONE*, *10*(8), 1–17. https://doi.org/10.1371/journal.pone.0136489

Oh, D. R., Kim, J. R., Choi, C. Y., Choi, C. H., Na, C. S., Kang, B. Y., Kim, S. J., & Kim, Y. R. (2019). Effects of ChondroT on potassium Oxonate-induced Hyperuricemic mice: Downregulation of xanthine oxidase and urate transporter 1. *BMC Complementary and Alternative Medicine*, *19*(1), 1–8. https://doi.org/10.1186/s12906-018-2415-2

Pavelcova, K., Bohata, J., Pavlikova, M., Bubenikova, E., Pavelka, K., & Stiburkova, B. (2020). Evaluation of the influence of genetic variants of slc2a9 (Glut9) and slc22a12 (urat1) on the development of hyperuricemia and gout. *Journal of Clinical Medicine*, *9*(8), 1–21. https://doi.org/10.3390/jcm9082510

Sharma, G., Dubey, A., Nolkha, N., & Singh, J. A. (2021). Hyperuricemia, urate-lowering therapy, and kidney outcomes: a systematic review and meta-analysis. *Therapeutic Advances in Musculoskeletal Disease*, *13*, 1–21. https://doi.org/10.1177/1759720X211016661

Triyono, A., Astana, W., Novianto, F., Zulkarnain, Z., Fitriani, U., Nissa, U., & Ardianto, D. (2020). *The Effect of Hyperuricemia Herbs Drink on the Quality of Life*. 26911. https://doi.org/10.26911/the7thicph.05.40

Yamanaka, H. (2012). Essence of the revised guideline for the management of Hyperuricemia and gout. *Japan Medical Association Journal*, *55*(4), 324–329.

Zell, S. C., & Carmichael, J. M. (1989). Evaluation of allopurinol use in patients with gout. *American Journal of Hospital Pharmacy*, *46*(9), 1813–1816. https://doi.org/10.1093/ajhp/46.9.1813