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ARTICLE

POTENTIAL OF RAMBUTAN-HONEY ANTIOXIDANTS IN REDUCING MALONDIALDEHYDE LEVELS AND REGENERATING HEPATOCYTE CELLS IN ISONIAZID-RATS INDUCED

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ABSTRACT

Hepatotoxicity induced by prolonged administration of antituberculosis drugs such as isoniazid (INH) is associated with the production of free radicals. Rambutan-honey, rich in catalase enzyme, flavonoids, and vitamin C, exhibits antioxidant and immunomodulatory properties. *This study purpose* to assess the effect of rambutan-honey on malondialdehyde (MDA) levels and hepatocyte cell numbers in INH-induced rats. *The research method* using in vivo experimental study with a randomized posttest-only control group design. Thirty Wistar rats were divided into five groups: negative control(G1), positive control(G2), and three groups treated with rambutan-honey at doses of 250 mg/kgBW(G3), 500 mg/kgBW(G4), and 1000 mg/kgBW(G5). MDA levels were measured using the TBARS method on days 15 and 23, while hepatocyte cell numbers were assessed through histopathological examination using Hematoxylin-Eosin. Data were analyzed using One-Way ANOVA followed by Post-Hoc test. *This study revealed* that rambutan-honey at doses of 250, 500, and 1000 mg/kgBW significantly reduced MDA levels compared to controls, with a simultaneous increase in hepatocyte cell numbers (p=0.001). *The conclusion of this research* is the potential of rambutan-honey as an antioxidant and hepatoprotective agent, possibly mediated by its flavonoid content, which may stimulate superoxide dismutase activity akin to catalase enzyme and vitamin C.

Keywords: Hepatocyte cell; Honey; MDA

АБСТРАКТ

Гепатотоксичность, вызванная длительным приемом противотуберкулезных препаратов, таких как изониазид (INH), связана с образованием свободных радикалов. Рамбутан-мед, богатый ферментом каталазой, флавоноидами и витамином С, проявляет антиоксидантные и иммуномодулирующие свойства. Цель данного исследования - оценить влияние рамбутан-меда на уровень малондиальдегида (МДА) и количество клеток гепатоцитов у крыс, подвергшихся INH-индуцированию. Метод исследования - экспериментальное исследование in vivo с рандомизированным дизайном «посттестовая группа - только контроль». Тридцать крыс Вистар были разделены на пять групп: отрицательный контроль (G1), положительный контроль (G2) и три группы, получавшие рамбутан-мед в дозах 250 мг/кг массы тела (G3), 500 мг/кг массы тела (G4) и 1000 мг/кг массы тела (G5). Уровень МДА измеряли методом TBARS на 15-й и 23-й дни, а количество клеток гепатоцитов оценивали путем гистопатологического исследования с использованием гематоксилин-эозина. Данные были проанализированы с помощью одностороннего ANOVA с последующим Post-Hoc тестом. Исследование показало, что рамбутан-мед в дозах 250, 500 и 1000 мг/кг массы тела значительно снижал уровень МДА по сравнению с контролем, при одновременном увеличении количества клеток гепатоцитов (p=0,001). Вывод данного исследования - потенциал меда рамбутан как антиоксидантного и гепатопротекторного средства, возможно, опосредованный содержанием флавоноидов, которые могут стимулировать активность супероксиддисмутазы сродни ферменту каталазе и витамину С.

Ключевые слова: Клетка гепатоцита; Мед; МДА

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INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*, which can infect the lungs and spread through a patient's cough droplets. The droplets pass through the mouth or nasal passages, upper respiratory tract, bronchi, and then reach the alveoli.[1] The long duration of tuberculosis treatment can potentially cause side effects such as hepatotoxicity (11%), rash (6%), and joint pain (2%).[2] Hepatotoxicity is the most common side effect, which is caused by the prolonged administration of antituberculosis drugs, including the activation of isoniazid (INH), leading to the formation of free radicals such as reactive oxygen species (ROS).[3] INH is metabolized into acetyl isoniazid by N-acetyltransferase 2(NAT_2), followed by hydrolysis to form acetyl hydrazine and then oxidized by cytochrome $P_{450}2E_1$ (CYP_2E_1) into an intermediate compound (*N-hydroxyacetylhydrazine*), a molecule that is unpaired (free radical).[4]

The increase in free radicals due to oxidative stress caused by long-term administration of antituberculosis drugs can be attenuated by antioxidants. The role of antioxidants is to bind reactive oxygen species (ROS) to prevent tissue damage, especially in the liver, which can lead to hepatotoxicity.[5] One of the natural ingredients used as traditional medicine and currently being studied in Indonesia is honey. There are various types of honey based on the origin of the flower nectar, one of which is rambutan honey derived from the nectar of rambutan tree flowers (*Nephelium lappaceum*), which is darker in color indicating a high antioxidant content and a more pleasant taste, and this honey is often used as a natural remedy empirically.[6] There have been a number of research that have suggested that rambutan honey has anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory properties.[7]

This is because rambutan honey contains catalase enzyme that can convert hydrogen peroxide enzyme, flavonoids, and vitamin C.[8] Based on the above, rambutan honey with its antioxidant content of flavonoids, polyphenols, vitamin C, and catalase enzyme can act as the body's first line of defense against ROS from lipid peroxidation that produces MDA in hepatocyte cells and liver tissue due to the known side effects of antituberculosis drugs, but has not been scientifically proven, thus the researchers want to examine the antioxidant activity and the effect of hepatocyte cell regeneration of rambutan honey.[9]

This study aims to determine the MDA levels and the number of hepatocyte cells in Wistar rat induced with isoniazid and treated with rambutan honey, which both serve as the antioxidant activity of rambutan honey.

MATERIAL AND METHODS

Experimental animal research was conducted at the Laboratory of Animal Experimentation, Laboratory of Biochemistry, and Laboratory of Pathology Anatomy, Faculty of Medicine, Universitas Jenderal Achmad Yani Cimahi Indonesia. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Padjajaran, with the approval number 1179/UN6.KEP/EC/2020.

Research Design

The research method using in vivo experimental study with a randomized posttest-only control group design. Blood MDA levels were examined using the TBARS method, while the regeneration of hepatocyte cells was assessed by counting the number of hepatocyte cells using Hematoxylin-Eosin staining.

Research Object

The sample size used was based on the calculation using Federer's formula, resulting in a total of 30 rats required for the study. All rats were randomly assigned to their respective groups using Completely Randomized Design method. The subjects of this study were Wistar rats (*Rattus norvegicus*) from the *Muridae* family obtained from the Biofarma animal development unit Bandung, with inclusion criteria including: male Wistar

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rats aged between 3 to 4 months, weighing 200-250 grams, healthy as indicated by active movement, normal eating and drinking habits, and responsive to stimuli, all obtained from the same breeding facility with the same rat feed and treatment. This study used a sample of 30 Wistar rats divided into 5 groups: negative control (G1), positive control (G2), group 3 induced with 400 mg/kgBW INH and given 250 mg/kgBW rambutan honey (G3), group 4 induced with 400 mg/kgBW INH and given 500 mg/kgBW rambutan honey (G4), and group 5 induced with 400 mg/kgBW INH and given 1000 mg/kgBW rambutan honey (G5).[10,11]

Research Materials

Rambutan honey is derived from the nectar of the rambutan tree's flowers (*Nephelium lapaceum*), a tropical fruit tree native to Southeast Asia. Rambutan honey taken from Pusat Perlebahan National Perum Perhutani Parung Panjang Bogor Indonesia. The materials used for induction in this study were isoniazid Merck Germany at a dose of 400 mg/kgBW given for 7 days to 24 rats and distilled water. The treatment materials were rambutan honey at doses of 250 mg/kgBW for 6 rats (Group 3) for 7 days, 500 mg/kgBW for 6 rats (Group 4) for 7 days, and 1000 mg/kgBW for 6 rats (Group 5) for 7 days. The materials used to examine MDA levels included 0.5 mL serum, 0.5 mL 30% trichloroacetic acid (TCA) (Merck Germany), 0.5 mL 10% TBA (Merck Germany), and ice water. The materials required for the preparation of liver histology preparations included tissue sections from terminated rats fixed using 10% neutral buffered formalin (BNF) Sigma-Aldrich, USA. The solutions used for making these preparations were absolute ethanol (Merck, Germany), xylene (Merck, Germany), paraffin (Merck, Germany), 99.5% glycerin (Merck, Germany), albumin, eosin solution (Merck, Germany), and hematoxylin solution (Merck, Germany).

Experimental Animal Treatment

The rats were adapted for 7 days. On the 8th day, the Negative Control Group (G1) was given standard pellet feed at 30 g/day/rat and water ad libitum without induction of isoniazid and without treatment of rambutan honey. Meanwhile, on the 8th day, the Positive Control Group(G2) and the Treatment Group (G3), (G4), (G5) were induced with 400 mg/kgBW INH orally dissolved in distilled water. After 7 days of INH induction, the rats were fasted for 24 hours, and then the MDA levels were examined. Subsequently, on the 16th day, Group 3 was given 250 mg/kgBW rambutan honey for 7 days, Group 4 was given 500 mg/kgBW rambutan honey for 7 days, and Group 5 was given 1000 mg/kgBW rambutan honey for 7 days. After 7 days of treatment, the rats were terminated with ketamine to examine the MDA levels in the blood of rats treated with rambutan honey.

MDA Level Examination

The examination of blood MDA levels was conducted using the TBARS method with a spectrophotometer. The principle of this MDA examination is that isoniazid will oxidize plasma lipids, which can be seen as an increase in MDA levels. Rambutan honey, which has antioxidant properties, will inhibit the oxidation of lipids. The absorbance of the formed supernatant will be read using a spectrophotometer (Shimadzu UV-Vis Spectrophotometer, model UV-1800) at a wavelength of λ 532 nm.[4]

After euthanasia, the liver organ was taken to prepare histopathological liver preparations. The method of preparing histopathological liver preparations is by staining with Hematoxylin & Eosin. The preparations were examined at magnifications of 100x and 400x, starting from the damaged side (usually found on the blood vessel side). The number of normal hepatocyte cells, parenchymal degeneration, hydropic degeneration, and necrosis was counted from the blood vessel side with a count of 20 cells. The number of normal cells was multiplied by

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1, parenchymal degeneration by 2, hydropic degeneration by 3, and necrosis by 4.

The total of all multiplied results was then divided by 20 assess the number of normal hepatocyte cells, to see the regeneration of hepatocyte cells, cells undergoing hydopic degenartion, PMN cells, and cells undergoing nectosis in hepatocytes after treatment with rambutan honey.[10]

Data Analysis

The data from this study will be statistically analyzed. Blood MDA levels using paired T-Test, one-way ANOVA, and Post Hoc Tukey with p>0.05. Hepatocyte regenerating data analysis using one-way ANOVA and Post Hoc Duncan with p<0.05.

RESULT

Distribution of mean values, standard deviation, range, and the difference in blood MDA levels of rats after isoniazid induction and after treatment with rambutan honey can be seen in Figure 1.

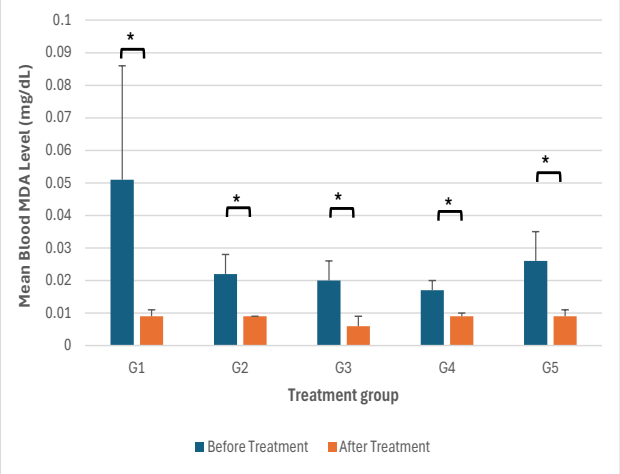

Figure 1. The difference in blood MDA levels of rats before and after treatment: negative control (G1) p=0.038, positive control isoniazid (G2) p=0.005, 250 mg/kgBW rambutan honey (G3) p=0.008, 500 mg/kgBW rambutan honey (G4) p=0.0013, 1000 mg/kgBW rambutan honey (G5) p=0.004.

The comparison of blood MDA levels before and after the administration of rambutan honey in the treatment groups (G3, G4, and G5) showed significant differences with p<0.05. The T-test results in Figure 1 indicate that all treatment groups experienced a decrease in blood MDA levels. This suggests that rambutan honey has a mechanism that can reduce blood MDA levels. The normality test using the Shapiro-Wilk test and the homogeneity test using the Levene test indicate that the data are normally distributed and homogeneous, with p>0.05. These results fulfill the assumptions for the One-Way ANOVA test, where the data variation is homogeneous. This, using the One-Way Anova test with a p vakue<0,05 is significantly different (Figure 2).

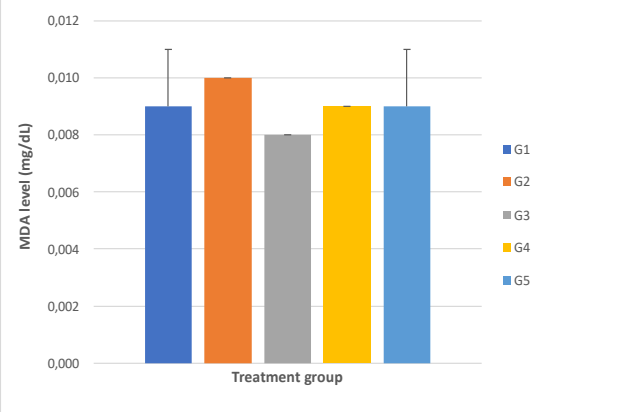

Figure 2. Effect treatment group negative control (G1), positive control isoniazid (G2), 250 mg/kgBW rambutan honey (G3), 500 mg/kgBW rambutan honey (G4), 1000 mg/kgBW rambutan honey on MDA levels with p=0,677.

The results indicate that rambutan honey has an effect in reducing the blood MDA levels of rats during the 7-day treatment. Rambutan honey at doses of 250 mg/kgBW, 500 mg/kgBW, and 1.000 mg/kgBW has been proven to reduce MDA levels. However, there was no significant difference between the treatment groups in terms of mean values after INH induction (0.051±0.035 mg/dL for G1, 0.022±0.006 mg/dL for G2, 0.020±0.006 mg/dL for G3, 0.017±0.003 mg/dL for G4, and 0.026±0.009 mg/dL for G5) and mean values after rambutan honey treatment (0.009±0.002 mg/dL for G1, 0.009±0.000 mg/dL for G2, 0.006±0.003 mg/dL for G3, 0.009±0.001

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mg/dL for G4, and 0.009±0.002 mg/dL for G5). This study demonstrates that rambutan honey can reduce blood MDA levels due to its role as an antioxidant and its content of catalase enzyme, flavonoids, and vitamin C.

Qualitative observations were made by assessing normal hepatocyte cells, cells with hydropic degeneration, polymorphonuclear cells (PMN), and cells with necrosis. Microscopic observations showed different results for each treatment group, as described in Figure 3.

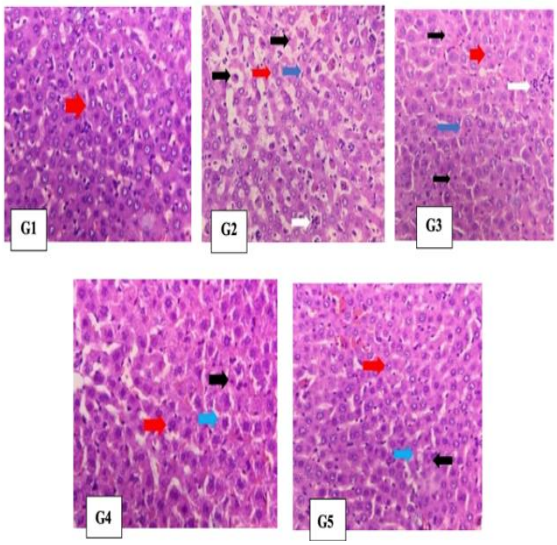

Figure 3. Histopathology of hepatocyte cells negative control (G1), positive control isoniazid (G2), 250 mg/kgBW rambutan honey (G3), 500 mg/kgBW rambutan honey (G4), 1000 mg/kgBW rambutan honey stained with Hematoxylin and Eosin (HE) in 5 high-power field (HPF) at 400x magnification.

A descriptive and analytical approach was taken in the process of carrying out the quantitative histopathological observation. Some of the parameters were found to have a normal distribution, while others did not, according to the findings of the tests for normality and homogeneity. Following the completion of the Shapiro-Wilk normality test, the data distribution was deemed to be normal, since the p-value was greater than 0.05. since a result, the data were subjected to a One-Way ANOVA test. A significant result was reached when the p-value was less than 0.05, as demonstrated in Figure 4, which is based on the One-Way ANOVA test. Significant findings indicate a difference between one or more groups.

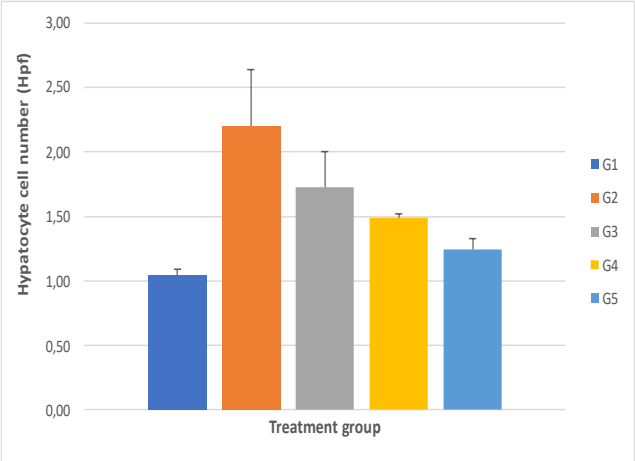

Figure 4. Effect of treatment group on hepatocyte cells number : negative control (G1), positive control isoniazid (G2), 250 mg/kgBW rambutan honey (G3), 500 mg/kgBW rambutan honey (G4), 1000 mg/kgBW rambutan honey with p=0. 000.

The results of the One-Way ANOVA analysis showed a significant difference with a p-value of <0.001 (p<0.05), indicating that the hypothesis is accepted (Figure 4). This suggests that there is regeneration of hepatocyte cells. To determine which dose of rambutan honey is better at enhancing hepatocyte cell regeneration, the analysis was continued with the Post Hoc Tukey. Comparison of the effects of rambutan honey on hepatocyte cell regeneration as seen from the number of normal hepatocytes. Statistically, the isoniazid group control and rambutan honey group 250 mg/kgBW (p=0.026) and 500 mg/kgB (p=0.000) p 1000 mg/kgBW (p=0.000) show a significant difference, indicating that starting from the 500 mg/kgBW dose, hepatocyte cell regeneration is evident based on the increased number of normal hepatocytes

DISCUSSION

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The results indicate that rambutan honey has an effect in reducing the blood MDA levels in rats during the 7-day treatment. This study proves that rambutan honey can reduce blood MDA levels as an antioxidant due to its content of catalase enzyme, flavonoids, and vitamin. Catalase is an enzyme that helps convert hydrogen peroxide into water and oxygen, thereby reducing oxidative stress in cells. Flavonoids are a group of plant compounds with antioxidant effects, which can help protect cells from damage caused by free radicals. Vitamin C, also known as ascorbic acid, is a potent antioxidant that can neutralize free radicals and regenerate other antioxidants in the body. Several studies have investigated the antioxidant properties of rambutan honey and its components. One study found that rambutan honey has a high total phenolic content, which contributes to its antioxidant capacity. Another study demonstrated that rambutan honey has significant antioxidant activity, as evidenced by its ability to scavenge free radicals and inhibit lipid peroxidation.[7]

Furthermore, the flavonoid content of rambutan honey has been studied for its potential health benefits. Flavonoids are known for their anti-inflammatory, antiviral, and anticancer properties. Vitamin C is also an important component of rambutan honey with antioxidant properties. Vitamin C plays a crucial role in boosting the immune system, promoting collagen production, and protecting cells from oxidative damage. Rambutan honey contains catalase enzyme, flavonoids, and vitamin C, which contribute to its antioxidant properties. These components help protect cells from oxidative stress and may offer health benefits such as reducing inflammation, boosting immunity, and reducing the risk of chronic diseases.[5,6,7] This research differs from the study conducted by Rachmat I. et al in 2017, where the subjects were white Wistar rats induced with alloxan. The effectiveness of rambutan honey in lowering blood glucose levels was evaluated in that study, showing that rambutan honey at a dose of 500 mg/kgBW effectively reduced the blood glucose levels in rats induced with alloxan.[11] The results of that study indicate that rambutan honey is effective in lowering blood glucose levels because it acts as an antioxidant, containing flavonoids and vitamin C, which are found to protect the pancreas from damage and potentially lower blood glucose levels in alloxan-induced diabetic rats. Vitamin C improves endothelium-dependent vasodilation in insulin-dependent diabetic rats.[12,13] The fructose, flavonoid, and vitamin C content in rambutan honey may lead to a decrease in blood glucose levels in diabetic rats. The difference between Rachmat I. et al's study and this study lies in the subjects and the induction agents used. In this study, the researcher used rats with hepatocyte damage induced by INH 400 mg/kgBW.

Antituberculosis medications like isoniazid are first-line. NAT2 enzymes in the liver and small intestine catalyze isoniazid acetylation, its major metabolic pathway. N-acetyltransferase 2 (NAT2) metabolizes INH to acetyl isoniazid, hydrolyzes it to acetyl hydrazine, and oxidizes it by cytochrome P450 (CYP2E1) to form an intermediate compound (N-hydroxy acetyl hydrazine), which is hepatotoxic because it is an unpaired (free radical) molecule that can bind to plasma protein cell hepatocytes.[14] The free radicals produced from this process will react with unsaturated fatty acids or polyunsaturated fatty acids (PUFAs) in cell membranes and plasma lipoproteins, a process known as lipid peroxidation. Polyunsaturated fatty acids (PUFAs) are degraded by free radicals, resulting in the final product, MDA.[15]

The study found that rambutan honey's antioxidants reduced blood MDA levels generated by isonioazid (INH). Rambutan honey has antioxidant activity because it contains flavonoids that can synthesize superoxide dismutase, which has the same role as catalase enzyme and vitamin C in the honey, which catalyze superoxide and its derivative, hydrogen peroxide. The catalase enzyme in rambutan honey functions to neutralize and accelerate the degradation of free radical compounds to prevent damage to cell macromolecule components.[16] Vitamin C

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is a non-enzymatic antioxidant, a natural compound that acts as a strong antioxidant and serves as a scavenger of free radicals. Vitamin C is water-soluble and can prevent oxidative stress that occurs in body tissues.[17]

The mechanism of flavonoids as antioxidants can be direct or indirect. Flavonoids act as antioxidants directly by donating hydrogen ions, thus neutralizing the toxic effects of free radicals. Flavonoids act as antioxidants indirectly by increasing the expression of endogenous antioxidant genes through several mechanisms. One of the mechanisms of increasing the expression of antioxidant genes is through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), resulting in an increase in genes involved in the synthesis of endogenous antioxidant enzymes.[18]

As hepatoprotectors, flavonoids directly capture ROS, restrict ROS renewal, and indirectly boost antioxidant enzyme activity.19 Flavonoids reduce ROS generation by inhibiting xanthine oxidase and NADPH oxidases and chelating metals (Fe2+ and Cu+) to block redox processes that produce free radicals.[20]

CONCLUSION

MDA levels are lower with 250, 500, and 1000 mg/kgBW rambutan honey than with negative and positive controls. At 500 and 1000 mg/kgBW, rambutan honey boosted normal hepatocyte cell counts, indicating regeneration. Rambutan honey at 500 and 1000 mg/kgBW decreased MDA and increased normal hepatocyte cells in rats, suggesting antioxidant and hepatoprotective effects. Neither dose outperformed 250 mg/kgBW. Rambutan honey may be an antioxidant because its flavonoids produce superoxide dismutase, like catalase and vitamin C. MDA levels drop and hepatocyte count rises.

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DECLARATIONS

Confilct of interest. The author declare no conflicts of interest or potential commercial background in this research

Additional Information. No additional information is available for this paper.

REFERENCES

1. Centers for disease control. Transmission and pathogenesis of tuberculosis.2016;7. Available from: https://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf. 2016. "Accessed on [date]" 3 March 2024.
2. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis.
3. Eur Respir J. 1996; Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis 9(10):2026-30. DOI: https://doi.org/10.1183/09031936.96.09102026
4. Zaw et. al. KatG 315 Mutation as a molecular determinant for isoniazid resistance in mycobacterium tuberculosis. Borneo Journal of Medical Sciences (BJMS). 2017; 11(1):1-12. DOI: https://doi.org/10.51200/bjms.v11i2.602
5. Yuslianti. ER. Pengantar radikal bebas dan antioksidan. DeePublish. 2017; 109. ISBN 978-602-453-456-1
6. Gaglani et.al. A pro-oxidant property of vitamin C to overcome the burden of latent Mycobacterium tuberculosis infection: A cross-talk review with Fenton reaction. Front. Cell. Infect. Microbiol. 2023; Vol 13. DOI: https://doi.org/10.3389/fcimb.2023.1152269
7. Yuslianti ER., Bachtiar BM., Sujiatmo AB., Suniarti DF., Sutjiatmo AB. Effect topical rambutan honey pharmaceutical grade on oral mucosa wound healing based on tissue wound closure and fibroblasts proliferation in vivo. International Journal of Pharmacology. 2015;

11 (7): 864-869. DOI: https://doi.org/10.3923/ijp.2015.864.869
8. Yuslianti ER, Bachtiar BM, Suniarti DF, Sutjiatmo AB. Effect of rambutan honey (Nephelium lappaceum) acute administration on mortality, body weight, toxicity symptoms and relative organ weight of Swiss webster mice. Research Journal of Medicinal Plants. 2016; 8 (1): 1-7. DOI: https://doi.org/10.3923/rjt.2016.1.7
9. Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. Pharmacognosy Res. 2017; 9(2):121-127. DOI: https://doi.org/10.4103/0974-8490.204647.
10. Chaudhary P et.al. Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. Front. Chem. Sec. Medicinal and Pharmaceutical Chemistr. 2023; Volume 11:1-24. DOI: https://doi.org/10.3389/fchem.2023.1158198
11. Ruan L., Fan J. T., Hong W, Zhao H, Li MH, Jiang L, Xing Wang JS. Isoniazid-induced hepatotoxicity and neurotoxicity in rats investigated by HNMR based metabolomics approach 2018. "Accessed on [date]" 15 March 2024. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29936297.
12. Rachmat I. I, Yuslianti E, Permatasari F, Koswara T. Antihyperglycemic effect of rambutan honey in alloxan-induced diabetic wistar rats. Research Journal of Toxicology. 2017; 12(1): 42-49. DOI: https://doi.org/10.3923/jpt.2017.42.49
13. Luan F, Peng L, Lei Z, Jia X, Zou J, Yang Y, He X, Zeng N. Traditional uses, phytochemical constituents and pharmacological properties of Averrhoa carambola L. A Review. Front Pharmacol. 2021 Aug 12;12:699899. DOI: https://doi.org/10.3389/fphar.2021.699899
14. Dewi, N.K.S.M.; Ramona, Y.; Saraswati, M.R.; Wihandani, D.M.; Wirasuta, I.M.A.G. The Potential of the Flavonoid Content of Ipomoea batatas L. as an Alternative Analog GLP-1 for Diabetes Type 2 Treatment-Systematic Review. Metabolites 2024, 14, 29. DOI: https://doi.org/10.3390/metabo14010029
15. Hassan HM, Yousef BA, Guo H, Xiaoxin L, Zhang L, Jiang Z. Investigating the CYP2E1 potential role in the mechanism behind INH/LPS-induced hepatotoxicity. 2018; 9: 198.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850051/. "Accessed on [date]" 15 March 2024. DOI: https://doi.org/10.3389/fphar.2018.00198
16. Cordiano, R., Di Gioacchino, M., Mangifesta, R. Panzera, C. Gangemi, S., Minciullo, P.L. Malondialdehyde as a potential oxidative stress marker for allergy-oriented diseases.: An update. Molecules. 20238:, 5979. DOI: https://doi.org/10.3390/molecules28165979
17. Vona, R; Pallotta, L; Cappelletti, M; Severi, C; Matarrese, P. The impact of oxidative stress in human pathology: focus on gastrointestinal disorders. AAntioxidants. 2021;, 10, 201. DOI: https://doi.org/10.3390/antiox10020201
18. Ilesanmi OB., Adeogun EF., Odewale TT., Chikere B. Lead exposure-induced changes in hematology and biomarkers of hepatic injury: protective role of TrévoTM supplement. Environ Anal Health Toxicol. 2022 Jun;37(2):e2022007-0. doi: DOI: https://doi.org/10.5620/eaht.2022007
19. Ullah A., Munir S., Badshah SL., Khan N., Ghani L., Poulson BG., Emwas AH., Jaremko M. Important flavonoids and their role as a therapeutic agent. Molecules. 2020 Nov 11; 25(22):5243. DOI: https://doi.org/10.3390/molecules25225243
20. Peng et,al. Protective effects and mechanisms of flavonoids in renal ischemia-reperfusion injury. Pharmacology. 2023;. 1087(1): 27-36. DOI: https://doi.org/10.1159/000527262
21. Dias MC., Pinto DCGA., Silva AMS. Plant flavonoids: Chemical characteristics and biological activity. Molecules. 2021 Sep 4; 26(17):5377. DOI: https://doi.org/10.3390/molecules26175377