Jurnal Riset Kesehatan, 13 (2), 2024, 136 - 144

DOI: 10.31983/jrk.v13i2.12112

Jurnal Riset Kesehatan

http://ejournal.poltekkes-smg.ac.id/ojs/index.php/jrk

IMPACT OF FRAGRANT PANDAN LEAVES ETHANOL EXTRACT (FPLEE) ON ALT AND AST LEVELS IN HIGH-FAT DIET-INDUCED RAT

Ni Made Wiasty Sukanty[a*] ; Farida Ariani[b] ; Lina Yunita[c]

[a,b,c] *Undergraduate Nutrition Study Program, Faculty of Health, Bumigora University ; Jl. Ismail Marzuki No.22, Cilinaya, Cakranegara ; Mataram 83127 ; Indonesia*

Abstract

Energy-dense, low-nutrient, and ultra-processed diets rich in fat can be a risk factor for fatty liver disease. Fragrant pandan is a plant that grows widely in Indonesia and is widely used as a herbal plant. This study aimed to determine the potential of fragrant pandan leaf ethanol extract (FPLEE) to reduce ALT and AST levels. It is a posttest control group design experiment. A total of 24 *Rattus norvegicus* specimens. All groups were given high-fat food for two weeks, except for NC. In the next two weeks, S was induced by simvastatin and FPLEE; T1, T2, and T3 were induced by 8, 16, and 32 mg/200 g BW/day, respectively. The One-Way ANOVA test results showed α=0.000 for ALT and α=0.029 for AST. Post-hoc LSD showed that NC was significantly different from T1, T2, and T3 ($p<0.05$); therefore, FPLEE was unable to reduce ALT levels. For AST levels, NC was significantly different from C+, T1, and T2 ($P<0.05$). Thus, T3 (32 mg/200 g BW/day of FPLEE) yielded the best results in reducing AST levels ($p>0.05$). Based on these results, FPLEE has side effects on liver function, as seen in increased blood ALT levels, but it can reduce blood AST levels.

Keywords: *Alanine Aminotransferase; Aspartate Aminotransferase; Fragrant Pandan Leaves Ethanol Extract; Liver; High-Fat Diet*

1. Introduction

Non-communicable diseases are the most common cause of death in society. This disease often occurs in developing countries, where economic growth has led to industrialization and urbanization. It causes a change in diet from a traditional diet to an energy-dense, low-nutrient, and ultra-processed diet that is generally rich in fat and can cause metabolic diseases (Kachwaha et al., 2024). Metabolic diseases are the most common diseases. A high-fat diet is closely associated with the emergence of metabolic diseases (Sukanty & Prijanti, 2021; Zhang, Ho, Wei, Xiao, & Lu, 2024).

In lipid metabolism, liver plays a role in cholesterol metabolism (Alviola, Fathurrahman, Rifai, & Afrah, 2023). Cholesterol is used to metabolize fat-soluble vitamins (vitamins A, D, E, and K) for the formation of steroid hormones and bile salts, which play a role in the absorption of fats and vitamins in the small intestine (Trisnawati, Djuang, & Hutapea, 2024). Excessive consumption of high-fat foods can lead to obesity. This condition is generally accompanied by nonalcoholic fatty liver disease (NAFLD), insulin resistance, dyslipidemia, and cardiovascular disease, which triggers de novo lipogenesis in the liver and impaired fatty acid transport. Excess fat will be stored in adipose tissue, but if the amount of fat continues to increase, the body will store it in nonadipose tissue, especially the liver. As a result, fatty liver occurs, known as steatosis. If left to continue, liver cirrhosis and even liver carcinoma will occur (Lian, Zhai, Li, & Wang, 2020). This condition is characterized by the increased activity and secretion of alanine aminotransferase (ALT) and

*) Corresponding Author (Ni Made Wiasty Sukanty)
E-mail: kanty@universitasbumigora.ac.id

DOI: 10.31983/jrk.v13i2.12112

aspartate aminotransferase (AST) enzymes produced by the liver into the blood circulation. Thus, the examination of ALT and AST levels can be a parameter for liver function disorders (W. C. W. Putri, Yuliawati, & Rahman, 2021).

ALT is an enzyme that transfers the amino group from alanine to a-ketoglutarate, producing pyruvate and glutamate, which are important for energy formation. Apart from being produced by the liver, ALT is produced by the heart, kidneys and muscles, but in small quantities. Thus, ALT is a specific marker of liver damage. Like ALT, AST is also produced by other organs such as skeletal muscle, heart muscle, kidneys and brain, but in greater quantities than ALT. AST transfers the amino group from aspartate to α-ketoglutarate, producing oxaloacetate and glutamate, which are important for energy formation (Kalas, Chavez, Leon, Taweesedt, & Surani, 2021).

Treatment for liver function disorders, such as fatty liver, involves maintaining cholesterol levels within the normal range, one of which is the use of medical drugs (Ngga et al., 2020). Long-term drug use can cause hepatotoxicity, myopathy, and renal failure (Kodariah & Wahid, 2020; W. C. W. Putri et al., 2021). In this regard, many people are turning to herbal plants because they are believed to have fewer side effects. This is increasingly supported by the echo of Back to Nature, which has increased research on herbal plants (Grenvilco D. Kumontoy, Deeng, & Mulianti, 2023).

The use of plants as medicinal ingredients has become widespread worldwide. Around 170 countries have regulations regarding herbal medicines (Zulkarnain, Triyono, Ardiyanto, & Saryanto, 2021). Indonesia is one of the countries with a wealth of herbal plants, and its regulations are regulated by the Food and Drug Monitoring Agency (Apriana et al., 2022). One plant that is believed to have many health benefits is the fragrant pandan (*Pandanus ammaryllifolius*). This plant proliferates in tropical regions. Research by Ulfah showed that fragrant pandan leaf ethanol extract (FPLEE) has a high phenolic (Ulfah, Sethyana, & Anam, 2023). Phenolic compounds can stabilize free radicals and inhibit lipid peroxidation. In Poorbagher et al.'s research, phenol obtained from nanoniosomes-loaded Myristica fragrans' can reduce ALT and AST levels in mice which induce hepatotoxicity (Poorbagher, Karimi, & Oskoueian, 2022). Other antioxidants in fragrant pandan leaves include flavonoids, alkaloids, saponins, tannins, and terpenoids (Oeleu, 2022). The ketone groups in flavonoids can react with the hydroxyl groups in cholesterol, thereby inhibiting cholesterol. Various antioxidant compounds in fragrant pandan leaves have been tested for their potential to reduce blood glucose levels, repair tissue damage, and heal burns (Lolok, Yuliastri, & Abdillah, 2020; Oeleu, 2022).

Although many studies have discussed the antioxidant potential of pandan leaves, its effect on ALT and AST levels in a high-fat diet is yet to be discovered. Based on this description, researchers wanted to determine the potential of ethanol extract from fragrant pandan leaves on the liver function of mice induced by a high-fat diet.

2. Method

This research has gone through an ethical test as proven by the research ethics code 053/EC-04/FK-06/UNIZAR/VII/2024. This research is a quantitative-experimental study with a posttest- control group design. The samples consisted of 24 rats divided into six groups: normal control (NC), positive control (C+), simvastatin (S), treatment 1 (T1), treatment 2 (T2), and treatment 3 (T3).

Fragrant pandan leaves extraction process

Fragrant pandan leaves were dried, baked in an oven at 40C, and then ground into powder. Fragrant pandan leafpowder was soaked in 96% ethanol at a ratio of 1:1 for three days then filtered, and evaporated to obtain an ethanol extract of fragrant pandan leaves (Hashary, Ibrahim, & Patma, 2022).

Composition of high-fat food

High-fat foods were prepared by mixing 80 g duck egg yolk, 5 g animal fat, and 15 g 65% sucrose. Food was given to the C+, S, T1, T2, and T3 groups of rats at 2 mL/200 g BW (Nurmeilis, 2015).

DOI: 10.31983/jrk.v13i2.12112

Preparation of simvastatin suspension

Simvastatin was prepared by dissolving 20.6 mg simvastatin in 100 mL distilled water. The dose administered to the rats was 0.206 mg/200 g rat body weight/day (Sukanty, Ariani, & Yunita, 2024).

Treatment of experimental animals

Biomedical-related research uses experimental animals like Rattus norvegicus. Treatment of experimental animals is carried out based on research ethics, which includes how to obtain experimental animals, transportation, maintenance, and techniques for carrying out trials, in this case, by minimizing the risk of discomfort to experimental animals (Biologi & Bioteknologi, 2023). All equipment used during the research was calibrated before use to provide accurate results.

In this study, rats underwent an acclimatization period of seven days in the laboratory, during which their body weights were recorded. The dosage of Fragrant Pandan Leaves Ethanol Extract (FPLEE) was determined based on the research by (Hashary et al., 2022) and administered using the once-a-day sonde method. The treatment protocol varied across six groups. The normal group received standard food for 28 days. The C+ group was fed high-fat food for 28 days. The simvastatin group was given high-fat food for 14 days, followed by standard food and simvastatin at a dose of 0.206 mg/200 g BW/day from days 15 to 28. The T1 group was fed high-fat food for 14 days, followed by standard food and FPLEE at a dose of 8 mg/200 g BW/day from days 15 to 28. Similarly, the T2 and T3 groups were given high-fat food for 14 days, then standard food combined with FPLEE at doses of 16 mg/200 g BW/day and 32 mg/200 g BW/day, respectively, from days 15 to 28. This treatment design aimed to evaluate the effects of FPLEE on alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in high-fat diet-induced rats.

Measurement of ALT and AST levels

On the 29th day, rats were anesthetized using ketamine, then blood was drawn from all groups via cardiac puncture. This aims to minimize pain in rats. Blood samples were placed into vacutainer tubes and centrifuged to collect the serum. ALT and AST examinations were performed using a biosystem machine in Awet Muda Narmada Hospital laboratory. This tool is a semi-autoanalyzer tool used for clinical chemistry examinations. This tool is always calibrated periodically.

Data analysis

The results of ALT and AST levels were analyzed for normality using the Shapiro-Wilk test. Differential tests for each group were performed using the One-Way ANOVA test followed by the post-hoc least significant difference (LSD) test with a confidence level of 95% ($\alpha = 0.05$).

3. Result and Discussion

Consumption of excessive amounts of cholesterol can increase blood cholesterol levels. This increase leads to the accumulation of lipids in the liver. If left untreated, it can cause liver damage. As a digestive organ, the liver produces both ALT and AST levels. These two enzymes play a role in protein metabolism in gluconeogenesis (Harahap, Harahap, & Sitorus, 2023; Susanti, Wiyanto, Hidayati, & Noor, 2024).

Jurnal Riset Kesehatan, 13 (2), 2024, 139 - 144

DOI: 10.31983/jrk.v13i2.12112

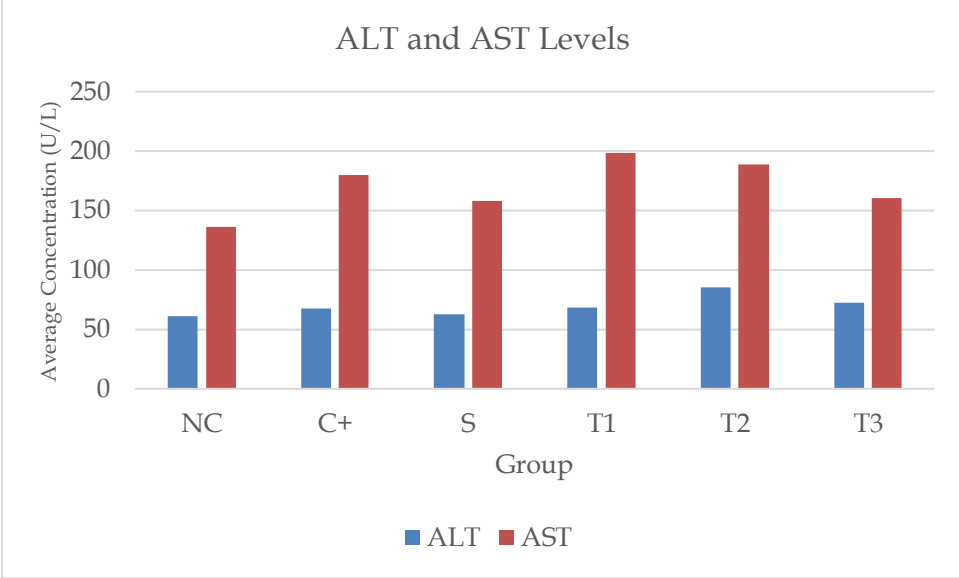

Figure 1. *Average measurements of ALT and AST levels in each group.*

ALT and AST levels were checked on the 29th day. Blood was collected from the heart and serum ALT and AST levels were measured. The examination results were tested statistically to determine the differences between the groups. Figure 1 displays the average ALT and AST levels in each group.

The detail results of ALT measurement are shown in Table 1. The lowest ALT levels were observed in NC, whereas the highest levels were observed in T2. The results of the One-Way ANOVA statistical test were p = 0.000, it indicates that there were at least two groups that had significant differences in ALT levels. To find out which groups are meant by these results, we carried out further tests using post-hoc least significant difference (LSD).

Table 1. ALT level.

Group	ALT Level Mean ± SD (U/L)	F (ANOVA)	p-Value
NC	60.975 ± 2.975	12.261	0.000***
C+	67.850 ± 3.496		
S	62.550 ± 3.516		
T1	68.700 ± 0.294		
T2	85.225 ± 9.979		
T3	72.625 ± 4.088		

***p < 0.001

Table 2 shows the post-hoc least significant difference (LSD) test for ALT levels. In this study, groups S, T1, T2, and T3 are expected to have a p value <0.05 against the NC group which indicates ALT concentrations that are similar to NC, in other words the administration of simvastatin and FPLEE is expected to be able to reduce ALT levels to close to the ALT value in the normal group. However, statistical test results show that there was a significant difference between the NC group and T1 (p=0.042), T2 (p=0.000), and T3 (p=0.004), while there was no significant difference in NC with C+ and S (p>0.05). Furthermore, the groups with other significant differences were T2 with C+, S, T1, and T3 (p<0.05).

DOI: 10.31983/jrk.v13i2.12112

Table 2. Differences in ALT levels between groups.

Group		Post-Hoc LSD p-Value
NC	C+	0.067
	S	0.661
	T1	0.042*
	T2	0.000*
	T3	0.004**
C+	S	0.151
	T1	0.813
	T2	0.000***
	T3	0.193
S	T1	0.099
	T2	0.000***
	T3	0.281
T1	T2	0.000***
	T3	0.281
T2	T3	0.002**

*p < 0.05
**p < 0.01
***p < 0.001

Similar to ALT, AST levels also showed One-Way ANOVA test results p < 0.05 (Table 3). Thus, there were at least two groups with significant differences. The lowest AST levels were observed in the NC group, followed by those in the S and T3 groups. The C+ group had lower levels than the T1 and T2 groups, but higher levels than the T3 group.

Table 3. AST level.

Group	AST Level Mean ± SD (U/L)	F (ANOVA)	p-Value
NC	136.075 ± 10.660	3.235	0.029*
C+	180.150 ± 35.789		
S	157.675 ± 15.562		
T1	198.275 ± 34.473		
T2	188.775 ± 28.539		
T3	160.825 ± 16.715		

*p<0.05

The test was continued with the post-hoc LSD test, where there were results in the form of a significant difference between the NC group and C+ (p = 0.025), T1 (p = 0.003), and T2 (p = 0.009). Additionally, group S was significantly different from group T1 (p = 0.037). Table 4 presents the results.

Table 4. Differences in AST levels between groups.

Group		Post-Hoc LSD p-Value
NC	C+	0.025*
	S	0.247
	T1	0.003**
	T2	0.009**
	T3	0.188
C+	S	0.230
	T1	0.329
	T2	0.639
	T3	0.299
S	T1	0.037*
	T2	0.102
	T3	0.864
T1	T2	0.606
	T3	0.053
T2	T3	0.139

*p<0.05
**p < 0.01

DOI: 10.31983/jrk.v13i2.12112

In this study, a high-fat diet (HFD) for two weeks did not increase ALT levels, as shown by the $p>0.05$ between the NC and C+ groups. These results align with the research by Liang et al., where HFD did not provide significantly different results for the normal and HFD groups. Apart from ALT, AST also yielded the same results as Liang et al. A high-fat and high-cholesterol diet (HFHCD) increased these two enzymes. HFHCD, which causes an increase in ALT and AST levels, shows that administering cholesterol directly can cause liver damage more quickly than a HFD without cholesterol (Liang et al., 2021).

However, in this study, the HFD increased blood AST levels, as evidenced by the significant difference in AST levels between the NC and C+ groups ($p<0.05$). ALT is synthesized by the liver, while AST is synthesized by the liver and extrahepatic tissues, such as the heart, kidneys, skeletal muscles, and erythrocytes (Yasar & Kokbas, 2024). Thus, liver function tests must test ALT and AST levels simultaneously to determine whether damage only occurs in the liver or extrahepatic tissue (Sovia, Kristiana, Nurdina, & Rachman, 2024).

The increase in AST levels in the C+ group, without being followed by an increase in ALT, appeared to be caused by an increase in AST produced by the extrahepatic tissue. When HFD is administered, lipid accumulation, oxidative stress, and inflammation can occur in the heart muscle, adipose tissue, kidneys, and skeletal muscle (Sztolsztener, Bzdęga, Hodun, & Chabowski, 2023). Damage to these various tissues causes the release of AST into the blood (Kendran, Gelgel, Anthara, & Anggreni, 2013).

In line with the ALT levels, which did not increase in the C+ group, the S group also showed the same results. Simvastatin is used to lower the blood cholesterol levels. It targets HMG-CoA reductase activity in the liver (Pieku´s-Słomka et al., 2023). Simvastatin can control blood cholesterol levels, thereby preventing fatty liver damage, which can increase ALT levels (Elleithi, El-Gayar, & Amin, 2023). The long-term use of simvastatin can damage cells, especially hepatocytes. An increase in ALT levels due to simvastatin was shown in the research of Abo-zalam et al. These results are supported by an increase in oxidative stress, characterized by reduced glutathione (GSH) and superoxide dismutase (SOD) activity, followed by a decrease in malondialdehyde (MDA) (Abo-zalam et al., 2021).

Administration of FPLEE at various concentrations to groups T1, T2, and T3 resulted in higher ALT levels than the NC group ($p<0.05$). This shows that the administration of HFD followed by FPLEE increases ALT levels. Steroids are one of the components of FPLEE. Steroids can interact with the cell membrane, resulting in decreased cell membrane integrity. As a result, the cells easily experience lysis (Jacky, Putri, & Azizah, 2019). ALT is an enzyme in the cytoplasm, so when cell leakage occurs, ALT will come out and be distributed in the blood (Kendran et al., 2013).

When administering simvastatin ($p>0.05$), a better protective effect on AST levels was observed than administering FPLEE at a concentration of 8 mg/200 g BW/day ($p<0.01$). Similar to T1, T2 showed high AST levels ($p<0.01$). The administration of ethanol extract had different effects on the parameters tested. This effect depended on the concentration of the ethanol extract. At low concentrations, ethanol extract can act as an antioxidant and anti-inflammatory agent, but at higher concentrations, ethanol extract can be toxic (Mulyana & Farida, 2022). Therefore, the optimum levels must be tested.

In the AST examination, FPLEE reduced AST levels on a concentration of 32 mg/200 g BW/day. FPLEE contains various antioxidants, such as flavonoids, tannins, and saponins (Hashary, Damayanti, Rusdiaman, & Nurzak, 2023). This antioxidant prevents the formation of free radicals due to lipid accumulation, which can cause oxidative stress. There are several antioxidant mechanisms to ward off free radicals, including antioxidants that bind to transition metals and antioxidants that prevent lipid oxidation by free radicals (Hasim, Hasanah, Andrianto, & Nur Faridah, 2018; Suryani, Murti, Ardiyan, & Setyowati, 2018). Thus, liver and extrahepatic tissue damage can be avoided, and AST levels do not increase.

Research by Hasim shows that flavonoids have antioxidant activity (Hasim et al., 2018). Likewise, research by Putri et al. tested that avocado seeds containing flavonoids and saponins reduced fat in the liver cells of hypercholesterolemic mice. Hypercholesterolemia triggers fat to accumulate in liver cells (F. Putri, Fachrezi, Kusmahardhika, Lzza, & Saputra, 2023). This condition can change the physical properties of cell membranes, causing Reactive Oxygen Species (ROS) leakage from mitochondria. If this continues, lipid peroxidation occurs, which causes increased ROS production and cell lysis, which triggers increased

DOI: 10.31983/jrk.v13i2.12112

release of AST into the blood. Antioxidants such as flavonoids, tannins and saponins can prevent cell damage by neutralizing ROS (Hasim et al., 2018).

Based on the research results above, the content of various antioxidants in FPLEE has different effects on ALT and AST levels. Different antioxidant mechanisms could cause this difference. Providing treatment over a short period can also contribute to the results. Therefore, it is necessary to conduct further research over a longer period to see the effects of FPLEE more accurately.

4. Conclusion and Suggestion

Induction of HFD in rats did not increase ALT levels, but increased blood AST levels. Giving FPLEE as a natural ingredient for lowering blood ALT levels is not recommended due to ALT levels actually increased in rats administered FPLEE at concentrations of 8, 16, and 32 mg/200 g BW/day. Based on these findings, FPLEE has side effects on liver function. However, FPLEE reduced blood AST levels. The optimal concentration of FPLEE for reducing blood AST levels was 32 mg/200 g BW/day. Further research is needed to explore the safety and efficacy of FPLEE and examine the mechanisms of ALT increase and AST decrease by FPLEE in the cellular and molecular fields.

5. Acknowledgments

The author would like to thank the Ministry of Education, Culture, Research, and Technology (Kemendikbudristek), Bumigora University, and all the people involved in this research who cannot be mentioned one by one.

6. References

Abo-zalam, H. B., El-Denshary, E. S., Abdelsalam, R. M., Khalil, I. A., Khattab, M. M., & Hamzawy, M. A. (2021). Therapeutic Advancement of Simvastatin-Loaded Solid Lipid Nanoparticles (SV-SLNs) in Treatment of Hyperlipidemia and Attenuating Hepatotoxicity, Myopathy and Apoptosis: Comprehensive Study. *Biomedicine and Pharmacotherapy*, *139*, 111494. https://doi.org/10.1016/j.biopha.2021.111494

Alviola, N. A., Fathurrahman, Z., Rifai, R. N., & Afrah, A. S. (2023). Sistem Diagnosa Penyakit Liver Menggunakan Metode Artificial Neural Network: Studi Berdasarkan Dataset Indian Liver Patient Dataset. *Jurnal Informatika: Jurnal Pengembangan IT (JPIT)*, *8*(3), 308–312. https://doi.org/10.30591/jpit.v8i3.5346

Apriana, M., Toni, R. M., Huda, M. C., Kamal, Z. M., Khoerunnisa, R., Allahuddin, A., … Anggraeni, F. (2022). Pengobatan Penyakit Kolestrol Dengan Menggunakan Ekstrak Herbal Di Indonesia - A Review. *Jurnal Buana Farma: Jurnal Ilmiah Farmasi*, *2*(2), 19–32. https://doi.org/10.36805/jbf.v2i2.383

Biologi, J., & Bioteknologi, F. (2023). Pelatihan Uji in Vivo Hewan Laboratorium Berbasis Penelitian Bidang Bioteknologi Kesehatan Pada Siswa SMA Pangudi Luhur Yogyakarta. *Seminar Nasional Pengabdian Kepada Masyarakat*, *8*(1), 252–255.

Elleithi, Y. A., El-Gayar, A. M., & Amin, M. N. (2023). Simvastatin Induces Apoptosis and Suppresses Hepatocellular Carcinoma Induced in Rats. *Applied Biochemistry and Biotechnology*, *195*(3), 1656–1674. https://doi.org/10.1007/s12010-022-04203-0

Grenvilco D. Kumontoy, Deeng, D., & Mulianti, T. (2023). Pemanfaatan Tanaman Herbal Sebagai Obat Tradisional Untuk Kesehatan Masyarakat di Desa Guaan Kecamatan Mooat Kabupaten Bolaang Mongondow Timur. *Jurnal Holistik*, *16*(3), 1–20.

Harahap, M. S., Harahap, U., & Sitorus, P. (2023). Uji Aktivitas ALT, AST dan Histopatologi Ekstrak Etanol Rimpang Temu Kunci (Boesenbergia rotunda (L.) Mansf) pada Tikus Putih Jantan. *Journal of Pharmaceutical and Health Research*, *4*(2), 173–182. https://doi.org/10.47065/jharma.v4i2.3262

Hashary, A. R., Damayanti, U. P., Rusdiaman, R., & Nurzak, A. N. (2023). Identifikasi Senyawa Antioksidan dari Ekstrak Etanol Daun Pandan Wangi (Pandanus amaryllifolius) dengan Metode 2,2-Diphenyl-1-Picryl-Hydrazyl (DPPH). *Jurnal Riset Kefarmasian Indonesia*, *5*(2), 204–215. https://doi.org/10.33759/jrki.v5i2.360

Hashary, A. R., Ibrahim, I., & Patma, C. (2022). Pengaruh Pemberian Ekstrak Etanol Daun Pandan Wangi (Pandanus amaryllifolius Roxb) Terhadap Kolesterol Mencit (Mus musculus). *Jurnal Novem Medika*

Farmasi, *1*(1), 1–8.

Hasim, H., Hasanah, Q., Andrianto, D., & Nur Faridah, D. (2018). Aktivitas Antioksidan dan Antihiperkolesterolemia In Vitro Dari Campuran Ekstrak Angkak dan Bekatul. *Jurnal Teknologi Dan Industri Pangan*, Vol. 29, pp. 145–154. https://doi.org/10.6066/jtip.2018.29.2.145

Jacky, Putri, D. A., & Azizah, M. (2019). Uji Aktivitas Anti Bakteri Ekstrak Etanol Daun Pandan Wangi (Pandanus amaryllifolius Roxb) Terhadap Bakteri Penyebab Diare. *Jurnal Kesehatan Saelmakers Perdana*, *2*(1), 91–98. https://doi.org/10.32524/jksp.v2i1.200

Kachwaha, S., Kim, S. S., Das, J. K., Rasheed, S., Gavaravarapu, S. R. M., Pandey Rana, P., & Menon, P. (2024). Behavior Change Interventions to Address Unhealthy Food Consumption: A Scoping Review. *Current Developments in Nutrition*, *8*(3), 102104. https://doi.org/10.1016/j.cdnut.2024.102104

Kalas, M. A., Chavez, L., Leon, M., Taweesedt, P. T., & Surani, S. (2021). Abnormal Liver Enzymes: A Review for Clinicians. *World Journal of Hepatology*, *13*(11), 1688–1698. https://doi.org/10.4254/wjh.v13.i11.1688

Kendran, A. A. S., Gelgel, K. T. P., Anthara, D., & Anggreni, L. D. (2013). Toksisitas Ekstrak Daun Sirih Merah pada Tikus Putih Penderita Diabetes Melitus. *Jurnal Veteriner*, *14*(4), 527–533.

Kodariah, L., & Wahid, A. A. (2020). Pengaruh Ekstrak Biji Ketumbar (Coriandrum sativum) Terhadap Kadar Trigliserida dan Gambaran Histologi Hati Tikus (Rattus novergicus) yang Diinduksi Oleh Pakan Tinggi Lemak. *Jurnal Biotek Medisiana Indonesia*, Vol. 9, pp. 47–54. https://doi.org/10.22435/jbmi.v9i1.3899

Lian, C. Y., Zhai, Z. Z., Li, Z. F., & Wang, L. (2020). High Fat Diet-Triggered Non-Alcoholic Fatty Liver Disease: A Review of Proposed Mechanisms. *Chemico-Biological Interactions*, *330*(August). https://doi.org/10.1016/j.cbi.2020.109199

Liang, H., Jiang, F., Cheng, R., Luo, Y., Wang, J., Luo, Z., … He, F. (2021). A High-Fat Diet and High-Fat and High-Cholesterol Diet May Affect Glucose and Lipid Metabolism Differentially Through Gut Microbiota in Mice. *Experimental Animals*, *70*(1), 73–83. https://doi.org/10.1538/expanim.20-0094

Lolok, N., Yuliastri, W. O., & Abdillah, F. A. (2020). Efek Antidiabetes Kombinasi Ekstrak Etanol Daun Pandan Wangi (Pandanus amaryllifolius Roxb.) Dan Daun Salam (Syzygium polyanthum Wight.) Pada Tikus Putih Dengan Metode Induksi Aloksan. *Jurnal Mandala Pharmacon Indonesia*, *6*(1), 13–29. https://doi.org/10.35311/jmpi.v6i01.52

Mulyana, L., & Farida, E. (2022). Pengaruh Ekstrak Bunga Sepatu (Hibiscus Rosa – sinensis L.) terhadap Kadar Asam Urat Tikus Putih Galur Wistar. *Indonesian Journal of Public Health and Nutrition*, *4*(2), 181–190. https://doi.org/10.15294/ijphn.v4i2.58886

Ngga, Y. M. A., Tallomanafe, D., & Nurina, L. (2020). Pengaruh Pemberian Ekstrak Etanol Kecambah Kacang Hijau terhadap Histopatologi Hati Tikus Putih (Rattus norvegicus) Galur Sprague Dawley yang Hiperkolesterolemia. *Cendana Medical Journal*, *8*(1), 491–500.

Nurmeilis. (2015). *Penentuan Profil Lipid-Kolesterol Pada Tikus Normal dan Tikus Hiperkolesterol Setelah Pemberian Ekstrak Herba Kumis Kucing (Orthosiphon stamineus)*. Universitas Islam Negeri Syarif Hidyatullah Jakarta.

Oeleu, K. Y. (2022). Uji Aktivitas Gel Ekstrak Daun Pandan Wangi (Pandanus amaryllifolius Roxb) Terhadap Penyembuhan Luka Bakar Buatan Pada Kelinci New Zealand. *Jurnal Ilmiah Kesehatan Ar-Rum Salatiga*, *6*(2), 51–57. https://doi.org/10.36409/jika.v6i2.151

Pieku´s-Słomka, N., Mocan, L. P., Shkreli, R., Grapă, C., Denkiewicz, K., Wesolowska, O., … Mocaner, T. (2023). Don't Judge a Book by Its Cover: The Role of Statins in Liver Cancer. *Cancers*, *15*(5100). https://doi.org/10.3390/cancers15205100

Poorbagher, M. R. M., Karimi, E., & Oskoueian, E. (2022). Hepatoprotective Effect of Nanoniosome Loaded Myristica Fragrans Phenolic Compounds in Mice-Induced Hepatotoxicity. *Journal of Cellular and Molecular Medicine*, *26*(21), 5517–5527. https://doi.org/10.1111/jcmm.17581

Putri, F., Fachrezi, G. F., Kusmahardhika, N., Lzza, J. N., & Saputra, lndra K. (2023). Comparison of the effectiveness of avocado seeds (Persea americana mill.) and roselle flowers (Hibiscus sabdariffa l.) As hypolipidemic ingredients in terms of liver histopathology and weight of hypercholesterolemia mice. *The 4th International Conference on Life Science And Technology (ICoLiST)*, *2634*(020112). https://doi.org/10.1063/5.0111601

Putri, W. C. W., Yuliawati, & Rahman, H. (2021). Uji Aktivitas Hepatoprotektor Ekstrak Etanol Daun Rambutan (Nephelium lappaceum L.) pada Mencit Putih Jantan yang Diinduksi Parasetamol. *Pharmacon: Jurnal Farmasi Indonesia*, *18*(2), 148–156.

DOI: 10.31983/jrk.v13i2.12112

Rahayu, A. S., Mendrofa, H. K., & Bo'Ne, A. (2023). Hiperkolesterolemia Pada Peserta Posyandu Lansia di Kampung Putali Distrik Ebungfauw Kabupaten Jayapura. *Journal Health & Science: Gorontalo Journal Health and Science Community*, *7*(3), 263–271.

Sovia, E., Kristiana, R., Nurdina, S., & Rachman, H. (2024). Hepatoprotective Effect of Cinnamon (Cinnamomum burmanii) Extract on Serum Aspartate Transaminase (AST) of Male Wistar Rats Induced With Isoniazid.pdf. *Acta Medical and Health Sciences*, *2*(3), 109–115. https://doi.org/10.35990/amhs.v2n3.p109-115

Sukanty, N. M. W., Ariani, F., & Yunita, L. (2024). The Effectiveness of Fragrant Pandan Leaves Ethanol Extract in Reducing Cholesterol Levels In High-Fat Diet-Induced Rats. *Biology, Medicine, & Natural Product Chemistry*, *13*(2), 505–509. https://doi.org/10.14421/biomedich.2024.132.505-509

Sukanty, N. M. W., & Prijanti, A. R. (2021). The Role and Regulation of FOXO1 in Carbohydrate Metabolism and Its Targeting in Metabolic Diseases. *Indonesian Archives of Biomedical Research*, *1*(2). https://doi.org/https://doi.org/10.55392/indarcbiores.v1i2

Suryani, C. L., Murti, S. T. C., Ardiyan, A., & Setyowati, A. (2018). Aktivitas Antioksidan Ekstrak Etanol Daun Pandan (Pandanus amaryllifolius) dan Fraksi-Fraksinya. *Agritech*, *37*(3), 271–279. https://doi.org/10.22146/agritech.11312

Susanti, N., Wiyanto, B., Hidayati, D. N., & Noor, R. J. (2024). Analisis Tingkat Pengetahuan, Sikap, Perilaku Masyarakat Terhadap Kolestrol. *PREPOTIF: Jurnal Kesehatan Masyarakat*, *8*(2), 3856–3865. https://doi.org/10.31004/prepotif.v8i2.30159

Sztolsztener, K., Bzdęga, W., Hodun, K., & Chabowski, A. (2023). N-Acetylcysteine Decreases Myocardial Content of Inflammatory Mediators Preventing the Development of Inflammation State and Oxidative Stress in Rats Subjected to a High-Fat Diet. *International Journal of Inflammation*, *2023*. https://doi.org/10.1155/2023/5480199

Trisnawati, R., Djuang, M. H., & Hutapea, J. (2024). The Effect of Binahong Leaf Extract on Reducing Cholesterol and Histopathological Features in the Liver. *Journal La Medihealtico*, *05*(01), 139–146. https://doi.org/10.37899/journallamedihealtico.v5i1.1098

Ulfah, M., Sethyana, F., & Anam, S. A. F. (2023). Potensi Antioksidan dan Kadar Total Fenolik Flavonoid Ekstrak Daun Pandan Wangi (Pandanus amarillyfolius Roxb.) Pada Variasi Pelarut. *Media Farmasi Indonesia*, *18*(2), 115–123. https://doi.org/10.53359/mfi.v18i2.227

Yasar, U., & Kokbas, U. (2024). Retrospective comparison of ALT-AST values of patients before and after the COVID-19 period in Ardahan province. *Medicine Science | International Medical Journal*, *13*(2), 395. https://doi.org/10.5455/medscience.2024.04.032

Zhang, W., Ho, C. T., Wei, W., Xiao, J., & Lu, M. (2024). Piperine Regulates The Ccircadian Rhythms of Hepatic Clock Gene Expressions and Gut Microbiota in High-Fat Diet-Induced Obese Rats. *Food Science and Human Wellness*, *13*(3), 1617–1627. https://doi.org/10.26599/FSHW.2022.9250137

Zulkarnain, Z., Triyono, A., Ardiyanto, D., & Saryanto. (2021). Uji Klinik Keamanan Ramuan Jamu Penurun Kolesterol. *Jurnal Kefarmasian Indonesia*, *11*(1), 8–16. https://doi.org/10.22435/jki.v11i1.3186