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The Influence of Salak Skin Ethanol Extract on the Lipid Profile, Il-6 and MDA Serum (Experimental Study on Male Rats of Wistar Strains Induced by High-Fat Diet)

Hanny Fuzi Lestari[1], Setyo Trisnadi[2], Danis Pertiwi[3], Wahyudi[4]

[1,4] Postgraduate student of Biomedical Sciences, Faculty of Medicine, Universitas Islam Sultan Agung, Jl Kaligawe KM 4 Semarang 50012

[2,3] Department of Biomedical Sciences, Faculty of Medicine, Universitas Islam Sultan Agung, Jl Kaligawe KM 4 Semarang 50012

ABSTRACT: Dyslipidemia is characterized by an increase in total cholesterol, triglycerides, LDL and a decrease in HDL. One of the consequences of endothelial dysfunction as a precursor to cardiovascular disease is induced by oxidative stress and inflammation, so this condition must be controlled. Dyslipidemia causes an increase in pro-inflammatory cytokines which play a role in oxidative stress and inflammatory processes. The aim of this study was to determine the effect of administering snake fruit ethanol extract on serum lipid profile, IL-6 and MDA levels in Wistar rats induced by a high-fat diet. The type of research is experimental with a Post Test Only Control Group Design research design. The research subjects used 36 Wistar rats, divided into 6 treatment groups, namely healthy control group (KS), negative control (K-), positive control with simvastatin (K+), 60 mg dose EEKS group (P1), 120 mg dose EEKS group (P2), and EEKS group dose 240 mg (P3). Examination on day 36 used blood serum ELISA method to analyze levels of lipid profile, IL-6 and MDA. There was a significant difference using the t test ($p<0.05$) in the average decrease in total cholesterol, LDL, triglyceride levels and increase in HDL levels. The results of IL-6 levels showed significant differences between groups using the one way anova test ($p<0.05$), the 120 mg dose had the lowest results but was not significantly different when compared to the K+ group using the post hoc LSD test ($p<0, 05$), while the results of MDA levels were significantly different using the Kruskal Wallis test ($p<0.05$), showing that the 240 mg dose had the same results as the simvastatin group using the Mann-Whitney test ($p<0.05$). Snake bark ethanol extract (EEKS) at a dose of 240 mg has the same effect as simvastatin by reducing total cholesterol, LDL, triglyceride levels and increasing HDL. EEKS reduces IL-6 and MDA levels in dyslipidemia conditions.

KEYWORDS: Salak bark extract, lipid profile, IL-6, MDA

I. INTRODUCTION

Dyslipidemia is characterized by an increase in total cholesterol, triglycerides, LDL and a decrease in HDL. One of the consequences of dyslipidemia is endothelial dysfunction as a precursor to cardiovascular disease induced by oxidative stress and inflammation, so the condition must be controlled. Dyslipidemia causes an increase in pro-inflammatory cytokines that play a role in oxidative stress and inflammatory processes.[1] Oxidative stress occurs when ROS is more than antioxidants so that the amount of ROS increases and results in tissue damage. Interleukin-6 (IL-6) is a proinflammatory cytokine used as a marker of tissue inflammatory processes. Oxidative stress causes an increase in ROS in the body leading to lipid peroxidation. An organic compound that is a marker of lipid peroxidation is MDA *(malondyaldehyde).*

World *Health Organization* (WHO) data shows the prevalence of dyslipidemia in 2008 at 37% in the male population and 40% in the female population and is considered responsible for 2.6 million deaths and causes another 29.7 million lives to experience helplessness each year[4]. In Indonesia, data released by RISKESDAS in 2013 shows that 35.9% of the Indonesian population aged 15 $\geq$ years has dyslipidemia where women are more than men and urban residents are more than rural areas. RISKESDAS data in 2013 also showed that 15.9% of the population aged $\geq$ 15 years had a proportion of LDL $\geq$ 190 mg/dl, 22.9% HDL levels $\leq$ 40 mg/dl, and 11.9% had triglyceride levels of 500 $\geq$ mg/dl [5]. Data from PAPDI in 2011 found that in Indonesia only 31.3% of dyslipidemia patients achieved the desired therapeutic target[6]. The use of statin drugs as gold standard has a good effect on the overall lipid profile. Statins are drugs that lower total cholesterol, triglycerides and LDL that are very effective in preventing

cardiovascular risk. Although statins are effective in reducing lipid profiles, long-term use of statins has the side effect of increasing liver enzyme levels in the first 5 months of therapy, especially in hepatitis B and C patients, in addition to 5% of statin users experiencing myopathy and kidney failure so statin use must be monitored.

Nuranti., *et al* (2015), in his research found that ethanol extract of salak fruit peel dose 210 and 840 mg / kg weight of mice was proven to reduce total cholesterol levels of mouse blood with the largest decrease of 23.72% (dose 840 mg / kgbb mice), but the activity was still smaller than simvastatin with a percentage reduction in total cholesterol levels of 42.08%. Therefore, studies with higher EEKS doses of 200, 400, 600 mg / 200 grams of rat weights are expected to prove a decrease in lipid profile levels, lowering IL 6 levels and MDA blood serum of male rats *wistar strains.*

Research on ethanol extract of salak fruit peel as an antioxidant is still very limited. Research conducted by Handayani., *et al* (2021) found that ethanol extract of salak fruit peel contains alkaloids 7.61 % w/w; flavonoids 0.041%w/w; tannins 1.18 %w/w; and saponins 2 %w/w. Ethanol extract of salak fruit peel dose 140 mg / kg body weight in rats has the effect of reducing blood glucose levels and ureal and creatinine. Kanon., *et al* (2012) found that ethanol extract of salak fruit peel 150 mg / Kg BB can reduce blood sugar levels of male white rats (*Rattus norvegicus*) induced sucrose. Putri's research (2020), showed that ethanol extract of salak fruit peel dose 0.075-0.225 g/200 g BB can reduce blood sugar levels of male white rats (*Rattus norvegicus*) induced alloxan. Valentino., *et al* (2021) in their research found that EEKS can reduce blood sugar levels of alloxan-injected rats with a p value of < 0.05, and the best dose is 600 mg / KgBB. Meanwhile, to reduce the body weight of rats who have been injected with alloxane, less significant results p > 0.05.

Datu., *et al* (2022) who conducted a study on the effect of giving salak juice (*Salacca zalacca*) on lipid profiles and body weight of hyperlipidemia and obesity model rats concluded that giving salak juice affects lipid profiles by reducing total cholesterol, triglyceride levels, LDL levels. Giving salak juice can also reduce the weight of obese rats and reduce blood glucose levels.

Antioxidants are an option in efforts to control dyslipidemia. Treatment and prevention of diseases with antioxidants is one of the therapeutic modalities that is not inferior to pharmacological or lifestyle approaches. Potent antioxidants are proven to overcome several diseases and even degenerative diseases that are not easy to handle.[8] Nature has provided ingredients that humans can consume to inhibit free radicals.

Indonesian people have traditionally used plants for health maintenance and disease treatment. One plant that has health benefits is salak (*Salacca zalacca*). Salak plants are known to contain beneficial secondary metabolite compounds, one of which has an effect as an antioxidant that can reduce the negative impact of free radicals.[37]

Secondary metabolites are a group of compounds synthesized by living things and used to support life. Secondary metabolites in the pharmaceutical field are specifically used as drug candidates, namely the structure of compounds that have biological activity in the form of therapeutic effects with minimal toxicity.[36] The results showed that only about 30% of subjects with dyslipidemia achieved the target of dyslipidemia treatment. It is necessary to make efforts to reduce lipid profile levels with natural substances. One effort that can be done is the use of statins but long-term use is reported to have side effects in the form of myopathy and kidney failure, so the use of this drug must still be monitored.[8] So that alternative therapies are needed that are comfortable, cheap and acceptable such as by using medicinal efficacious materials that are around. Fruits are the best source of antioxidants for humans. Recent epidemiological studies have shown a positive correlation between the consumption of fruits rich in natural antioxidants and a reduced incidence of non-communicable diseases including cancer, cardiovascular disorders and diabetes[37]. One plant that can be used is salak. Salak is one of the horticultural commodities that has the potential to be developed commercially. Salak is a source of vitamins, minerals, fiber and bioactive components such as antioxidants. Salak is found in many tropical countries including in Indonesia. Salak peel contains several chemical compounds including polyphenols, flavanols, flavonoids, ascorbic acid and tannins that have activity as antioxidants.[3]

Salak fruit has been shown to have antioxidant effects, while research on the effects of salak fruit skin is still limited. People use salak in their fruit flesh, while other parts such as fruit skins are underused and even just thrown away and become useless waste. Though basically all parts of the plant such as fruit skin that are often overlooked, may have benefits. Existing studies on the effects of salak [Salacca zalacca (Gaertner) Voss] are more directed towards the flesh of the fruit. According to the results of research in salak fruit contains total polyphenols of 217.1 ± 13.2 mg GAE (gallic acid equivalent) / 100 g fresh weight[38]. Salak fruit has antioxidant activity measured by DPPH and ABTS methods of 110.4 ± 7.9 and 1507.5 ± 70.1 µM TE (micromolar trolox equivalent) / 100 g fresh weight, respectively. Ethyl acetate extract of salak var. Hunchback has antioxidant activity with IC50 1.6 µg/mL and methyl-pyrrole-2,4-dicarboxylic acid compounds are new compounds in the var salak plant. Hunchback that has antioxidant activity with IC50 3.27 µg/mL. While research on salak fruit skin is still little reported. According to research by Deng (2012), salak fruit peel has antioxidant activity with FRAP (Ferric-Reducing Antioxidant Power) value of 0.74 ± 0.10 µmol Fe(II) / g, TEAC (Trolox Equivalent Antioxidant Capacity) value of 4.50 ± 0.22 µmol Trolox / g fruit skin (Deng, et.al., 2012). Research conducted by Fitri

(2014) EEKS dose has antioxidant activity with IC50 value of 229.27 ± 6.35 (µg / mL). So far research explaining the effect of salak bark ethanol extract in rats on lipid profile levels, IL-6 and MDA is still limited. Therefore, research is still very relevant for further research.

The use of experimental male rats of *the wistar* strain because of genetics, physiology, and metabolism similar to humans. In addition, male rats of *the wistar* strain have a relatively short life cycle, a large number of offspring per birth, and ease of handling[9].

II. MATERIAL AND METHOD

Study Design and Experimental Animals

This research is a *true* research of *laboratory experiments in vivo* with the design of *Post Test Only Control Group Design*. The study subjects used 36 male rats of the 8-week-old Wistar strain weighing between 150-200 grams that met the inclusion and inclusion criteria, adapted for 7 days. This study used 6 treatment groups, a healthy control group with standard feed diet + aquabidest (K S), a negative control group with a high-fat feed diet without standard drug intervention + aquabidest (K -), a positive control group with a high-fat feed diet intervened with simvastatin dose 0.18 mg / day orally + aquabides for 14 days (K +), treatment group with high-fat feed diet for 14 days and administration of salak skin ethanol extract dose of 60 mg / 200 grams of rat body weight + aquabidest for 14 days (P1), and treatment with high feed diet for 14 days and administration of salak skin ethanol extract dose of 120 mg / 200 grams of rat body weight + aquabidest for 14 days (P2). The treatment group was given a high-feed diet for 14 days and ethanol extract of salak peel at a dose of 240 mg / 200 grams of rat body weight + aquabidest for 14 days (P3). On day 36, male wistar rats had their blood drawn to check lipid profile, IL-6 and serum MDA levels.

Research Materials

This research uses equipment consisting of Salak Skin Ethanol Extract doses of 60, 120, and 240 mg/200 grams of rat weight, rat serum*, Automatic Analyze Shimatzu brand*, 0.37% TBA solution in 0.25 N HCl, 15% TCA solution, and IL-6 kit reagent.

Research Equipment

This research uses equipment consisting of rat cage with feed holder with size L: 40 cm, W: 30 cm, H: 30 cm, rat scales "Nigushi Scale", small scissors, razor blade, oral sonde, gloves, cotton counter, drip pipette, *Eppendorf* tube, cuvet*, waterbath* with temperature 950C, spectrophotometer, centrifuge, micropipette, ELISA reader, and digital camera.

Salak Skin Ethanol Extract

Making salak peel extract using a re-maceration technique, where the salak skin that has been belnder, is weighed first for 150 gr and then extracted with 900 ml of 70% ethanol solution using a soaking technique of approximately 5 days. The extract is then filtered using filter paper (the results of the first filter) and the rest is extracted again in 2 days using 70% ethanol as much as 600 ml and then filtered again (the results of the second filter). Furthermore, the results of the first and second filters in the form of solution are collected and evaporated using a vacuum evaporator with a temperature of 700C until the volume becomes a quarter of the initial volume and continued again by drying it in the oven at 400C until it is a thick extract. Obtained 4.86 grams of thick extract and then divided into 3 concentrations: 200mg / kgbb, 400 mg / kgbb and 600 mg / kgbb.

Induction of Dyslipidemia

A high-fat feed diet is given standard feed and gastric swabs. The composition of high-fat feed consists of standard feed: egg yolk is carried out on the 8-21st day of treatment.

How to Sample Experimental Animals

(1) After 35 days of treatment, rat blood collection was carried out through puncture of the optalmica vein in the retro-orbitalis. **(2)** Blood is collected into the *collect tube.* The blood in the *collect tube* is allowed to stand first for 20 minutes, then centrifuge at a speed of 3000 rpm for 10 minutes until serum is formed, which is a clear liquid in the supernatant. The serum is taken and transferred to a test tube for analysis.

Lipid Profile Rate Measurement Procedure

(1) Prepare blanks, standards and samples of rat blood serum. **(2**) Put 1000 µl of total cholesterol, HDL, LDL, triglyceride test reagents into the tube (1000µl each three tubes). **(3)** Put a standard sample of total cholesterol, HDL, LDL, triglycerides as much as 10 µl into a tube containing 1000 µl of total cholesterol reagents, HDL, LDL, triglycerides. **(4)** Put a serum sample of 10 µl into total cholesterol, HDL, LDL, triglyceride reagents. **(5**) Incubation for 10 minutes at 370 C. **(6)** After 60 minutes, read using a spectrophotometer with a wavelength of 546 nm.

How to Measure IL-6 Rate

(1) Prepare reagents, samples and standard solutions. Try to be at room temperature +- 30 minutes before the solution is used. **(2)** Take plates and strips containing wells as needed, for unused strips can be stored in coolers with a temperature of 2-80C. **(3)** Put 50 µl of standard solution into the contribution, note: there is no need to add antibody, because in standard solution already contains antibody. **(4)** Put 40 µl of sample into the well and add 10 µl of anti-IL-6 antibody into the well containing the sample, then add 50 µl of streptavidin-HRP into the standard well and sample (except control negative), mix the solution and cover with a sealer then incubate in an incubator at 370C for 1 hour. **(5)** Open the sealer and wash the wells for 5x with a washing buffer of 0.35 ml each well until the well is full, and absorb it using a tissue to dry. **(6**) Put 50 µl of substrate A solution and 50 µl of substrate B into the drain, cover the plate using a sealer, then incubate into the incubator with a temperature of 370C with closed conditions (dark) for 10 minutes (until the solution changes from clear to blue). **(7)** Remove the plate containing the well, add 50 µl of stop solution to the sump, the solution will change from blue color to kining, then insert the plate into the elisa reader to read the color absorbance with a reading wavelength of 450 nm (valid result if the reading is done under 10 minutes).

How to Measure MDA Rate

(1) Blood of male wistar rats is taken as much as 1 ml through the orbital sinuses. **(2)** Blood samples are centrifuge at a speed of 3000 rpm for 30 minutes, then a supernatant of 200 µl is taken into the centrifuge tube. Added 15% TCA solution as much as 2000 µl and 0.37% TBA solution in 0.25N HCl as much as 2000 µl. **(3)** Heated through a *waterbath* with a temperature of 950C for 60 minutes. **(4)** Cooled to a temperature of 300C and put into the column Sep-Park C18. **(5)** Before use, the column is washed first using 5 ml *methanol* and water and then discarded. **(6)** The sample mixture is put into the column and discarded. **(7)** TBA is diluted from the column by adding 4 ml of methanol and then accommodated in a cuvet. **(8)** Color density is read using spectrophotometry at a wavelength of 532 nm.

III. RESULT

Lipid Profile Level Validation

Examination of lipid profiles of rat serum was carried out after administration of a high-fat diet (as validation) on day 21 of the study. The lipid profile levels examined were total cholesterol, LDL *(Low-density lipoprotein*), TG (Triglyceride), and HDL (*High-Density Lipoprotein*).

Table 1. Comparison of mean lipid profile levels of the non-suspension group with the high-fat diet interpense group

Group	Up to Cholesterol (mg/dL)	Up to LDL (mg/dL)	Triglyceride up to (mg/dL)	Up to HDL (mg/dL)
Group without interruption				
Mean ± SD	91.92 ± 16.92	37.8 ± 8.84	48.7 ± 20.7	44.43 ± 10.42
Shapiro-Wilk	0.69*	0.22*	0.9*	0.49*
Suspension group				
Mean ± SD	121.78 ± 16.33	65.39 ± 8.72	183.55 ± 25.41	20.00 ± 4.74
Shapiro-Wilk	0.69*	0.22*	0.90*	0.49*
Leuvene Test	0,95+	0,83+	0,25+	0,08+
the test	0,01^	0,00^	0,00^	0,00^

Description: The * sign indicates the result of normal data distribution (p > 0.05). The + sign indicates homogeneous data with the Levene test (p > 0.05). The ^ mark indicates a significant result for the *One Way Anova test* (p < 0.05)

A total of 6 group rats without interference (healthy group) and 6 group mice with high-fat diet interference were taken blood on day 21 to check lipid profile levels. The average total cholesterol yield in the group without interference was 91.92 mg / dL, compared to the intervention group increased by an average of 121.78 mg / dL. LDL levels in the group without interference 37.8 mg / dL, increased in the interpense group 65.39 mg / dL.Average triglyceride levels in the group without interference 48.7 mg / dL, increased in the interpense group with an average of 183.55 mg / dl, and decreased the average HDL levels from the group without interference 44.43 mg / dL, decreased in the interpense group to 20.00 mg / dL in the interpense group.

Analysis using the *Shapiro-Wilk test* is known to all normally distributed groups with values (p>0.05), and has homogeneous data variance with Leuvene Test results (p>0.05). Analysis of the t-test test obtained results (p< 0.05) in the group with the suspension

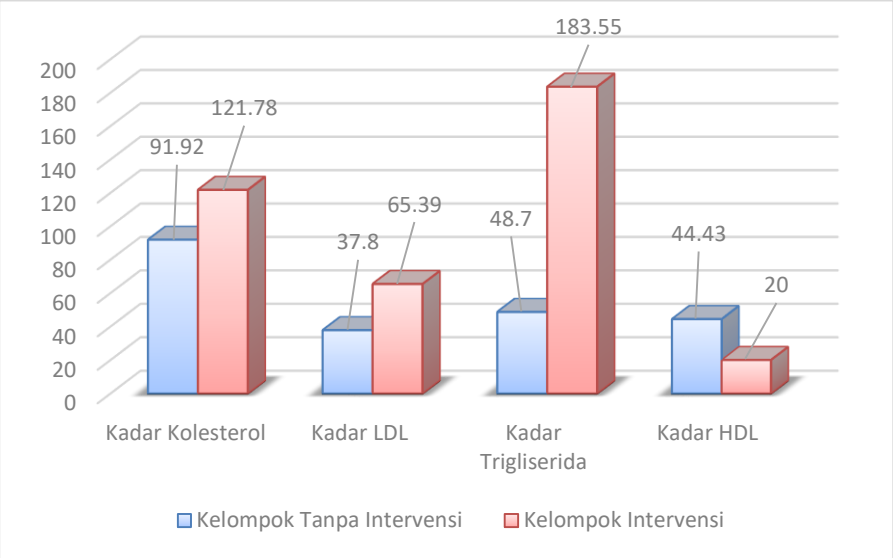

Figure.1. Graph of differences in lipid profile levels of the non-interference group with the high-fat diet interpense group

known to be significantly different for the four groups. Cholesterol, LDL and triglyceride levels increased after a high-fat diet and decreased HDL levels. Thus it can be concluded that the induction treatment of a high-fat diet is successful (there is a difference).

Results of lipid profile examination, IL-6 and MDA after EEX administration

Examination of lipid profiles, IL-6 and MDA from mouse serum was carried out after EEKS administration on day 36 of the study for 14 days. The lipid profile levels examined after EEKS administration were total cholesterol, LDL, Triglyceride, and HDL, then IL-6 and MDA parameters.

Table 2. Results of analysis of average lipid profiles, IL-6 and MDA

Variable		Group						
		KS	Towards-	K+	P1	P2	P3	*P value*
Total Cholesterol Up (mg/dL)	Mean ± SD	38.52 ± 25.48	46.35 ± 19.94	64.58 ± 6.63	71.02 ± 8.68	44.52 ± 9.35	67.83 ± 4.38	
	Shapiro-Wilk	0,17*	0,74*	0,85*	0,25*	0,97*	0,36*	
	Leuvene Test							0,003+
	One way Anova							0,019^
Up to LDL (mg/dL)	Mean ± SD	3.73 ± 0.92	6.72 ± 1.28	6.91 ± 2.15	7.98 ± 0.84	7.47 ± 2.33	8.97 ± 0.66	
	Shapiro-Wilk	0.08*	0.06*	0.60*	0.09*	0.34*	0.1*	
	Leuvene Test							0.04+
	One way anova							0,003^
Triglyceride up to (mg/dL)	Mean ± SD	55.12 ± 20.84	125.89 ± 31.12	68.75 ± 19.56	103.45 ± 8.36	44.61 ± 9.86	41.03 ± 4.00	
	Shapiro-Wilk	0.08*	0.06*	0.60*	0.09*	0.34*	0.10*	
	Leuvene Test							0.02
	One way anova							0,00^
Up to HDL (mg/dL)	Mean ± SD	23.77 ± 17.25	14.45 ± 0.89	43.92 ± 12.71	42.35 ± 5.46	28.13 ± 5.96	50.65 ± 7.97	
	Shapiro-Wilk	0.30*	0.65*	0.81*	0.99*	0.46*	0.36*	
	Leuvene Test							0.03
	One way anova							0,00^
Up to IL-6 (ng/L)	Mean	3.07 ± 1.01	4.02 ± 0.9	3.35 ± 0.93	4.36 ± 0.87	2.9 ± 0.55	3.8 ± 0.59	

	Shapiro-Wilk	0.5*		0,78*		0.93*		0,27*		0,89*		0,45*	
	Leuvene Test												0.68+
	One way Anova												0.032^
Up to MDA (mg/mL)	Mean	0.13	± 0.04	0.07	± 0.01	0.08	± 0.01	0.11	± 0.02	0.09	± 0.02	0.08	± 0.01
	Shapiro-Wilk	*0.12		*0.55		*0.42		0.01		0.01		*0.10	
	Leuvene Test												0.03
	Kruskal Wallis												0.01”

Description: the * sign indicates the result of normal data distribution ($p > 0.05$). The $^+$ sign indicates homogeneous data with the Levene test ($p > 0.05$). The ^ mark indicates a significant result for the *One Way Anova test ($p < 0.05$)*, The " mark indicates a significant result for the Kruskal Wallis test ($p < 0.05$).

A. Results of total cholesterol level examination after EEX administration

The average results of checking total cholesterol levels in the group after EEKS administration obtained results, namely in the KS group 38.52 mg / dL, K- 46.35 mg / dL, K + 64.58 mg / dL, P1 44.52 mg / dL, P2 67.83 mg / dL and P3 43.44 mg / dL. Total cholesterol levels were highest in the P1 group and the lowest group was the KS group. Descriptive analysis using the Shapiro-Wilk test is known to all normally distributed groups with a value of ($p>0.05$), but has inhomogeneous data variance with the results of the Leuvene Test ($p>0.05$) obtained results of 0.00. A graph of the average total cholesterol levels between groups is presented in Figure 2 below:

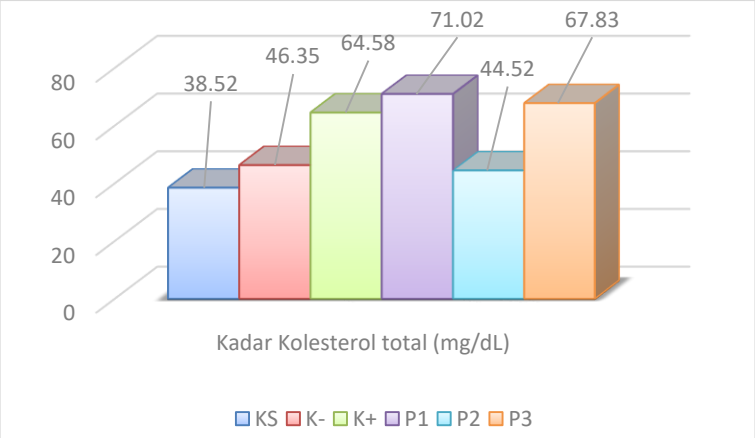

Figure 2. Average total cholesterol levels between groups after EEKS administration

Total cholesterol levels after EEX administration with a high-fat diet in the treatment group lowered total cholesterol levels. The group after EEKS was given the One way Anova test obtained results of 0.019 ($p < 0.05$) showing significant differences in each group after EEKS administration. Results can be seen in table 3.

Table 2. Differences in average total cholesterol levels of each group after EEKS administration with *Posh Hoc Tamhane test*

Group	Towards-	K+	P1	P2	P3
KS	1.00	0,87	0,70	1,00	0,80
Towards-		0,93	0,73	1,00	0,84
K+			0,99	0,20	1,00
P1				*0,08	0,13
P2					0,31

Description: * Means $p<0.05$

Analysis of the difference in average cholesterol levels was carried out *Post hoc Tamhane* test to determine the most influential EEKS dose. The results showed a significant difference in the P1 group compared to the P2 group with a result of 0.08 ($p < 0.05$), It can be concluded that the P2 group with a dose of 120 mg EEKS most affected total cholesterol levels in male rats *Wistar* strain induced by a high-fat diet.

B. Results of LDL level examination after EEKS administration

The average results of LDL levels in the group after EEKS administration obtained results in the KS group 3.73 mg / dL, K- 6.72 mg / dL, K + 6.91 mg / dL, P1 7.98 mg / dL, P2 7.47 mg / dL and P3 8.97 mg / dL. LDL levels were highest in the P3 group and the lowest group was the KS group. Descriptive analysis using the *Shapiro-Wilk test* is known to all normally distributed groups with a value of (p>0.05), but has inhomogeneous data variants with Leuvene Test results (p>0.05) obtained results of 0.04 , as in graph 3.

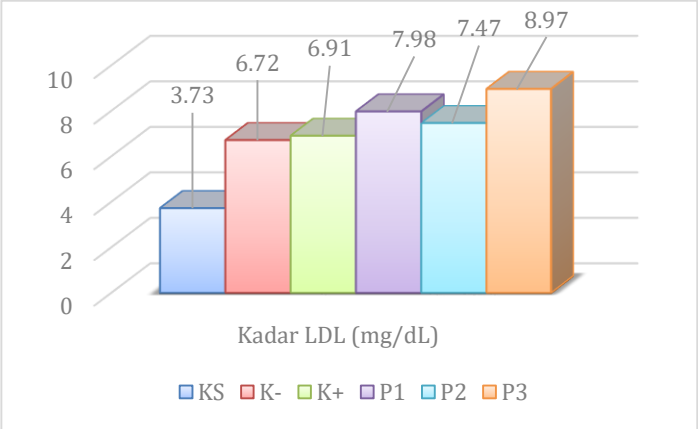

Figure 2. Average LDL levels between groups after EEKS administration

Analysis of the difference in average LDL levels carried out by Tamhane Post hoc *test showed that there was a significant difference in the KS group with P1 0.007 (p < 0.05), the KS group was significantly different from the P3 group with a value of 0.002 (p < 0.05), It can be concluded that the P3 group with a dose of 240 mg EEKS most affected LDL levels in male rats* of the wistar strain induced by a high-fat diet. Attached to table 4 follows:

Table 3. Differences in average LDL levels in each group after EEKS administration with Posh Hoc Tamhane test

Group	Towards-	K+	P1	P2	P3
KS	0,15	0,55	*0,007	0,47	*0,002
Towards-		1,00	0,93	1,00	0,37
K+			1,00	1,00	0,91
P1				1,00	0,84
P2					0,99

Keterangan: * Bermakna p<0,05

C. Results of triglyceride level examination after EEX administration

The average results of triglyceride levels in the group after EEKS administration obtained results, namely in the KS group 55.12 mg / dL, K- 125.89 mg / dL, K + 68.75 mg / dL, P1 103.45 mg / dL, P2 44.61 mg / dL and P3 41.03 mg / dL. Triglyceride levels were highest in the K+ group and the lowest group was the P3 group. Descriptive analysis using the Shapiro-Wilk test is known to all normally distributed groups with a value of (p>0.05), but has inhomogeneous data variants with the results of the Leuvene Test (p>0.05) obtained results of 0.02. as in the following chart 4:

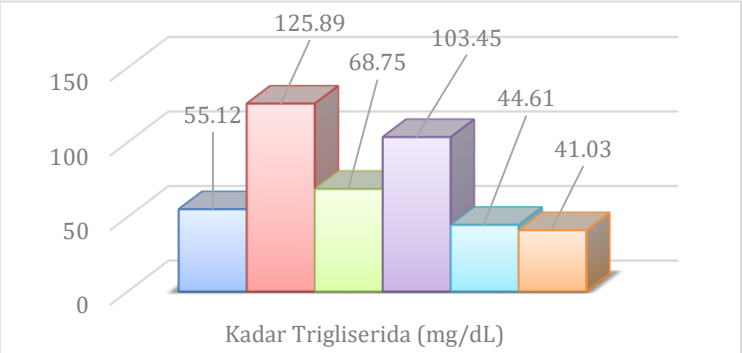

Figure 3 . Average triglyceride levels between groups after EEX administration

Descriptive analysis using the Shapiro-Wilk test is known to all normally distributed groups with a value of (p>0.05), but has inhomogeneous data variants with the results of the Leuvene Test (p>0.05) obtained results of 0.02.

Analysis of the average difference in triglyceride levels carried out by Tamhane Post hoc *test showed that there were significant differences in the KS group with K+ 0.003, K+ with P2 0.003, K+ with P3 0.010, P1 with P2 0.002 , P1 with P3 0.002 (p<0.05), It can be concluded that the P2 group with a dose of 120 mg and P3 with a dose of 240 mg EEKS most affected triglyceride levels in male rats of* the Wistar strain induced high-fat diet with the same level of meaning. Attached to table 5 follows:

Table 4. Differences in average LDL levels in each group after EEKS administration with *Posh Hoc Tamhane test*

Group	Towards-	K+	P1	P2	P3
KS	0,16	*0,003	0,18	1,00	0,99
Towards-		0,64	0,99	0,14	0,16
K+			0,05	*0,003	0,010
P1				*0,002	*0,002
P2					1,00

Description: * Means p<0.05

D. Results of HDL level examination after EEKS administration

The results of the average examination of HDL levels in the group after EEKS administration obtained results, namely in the KS group 23.77 mg / dL, K- 14.45 mg / dL, K + 43.92 mg / dL, P1 42.35 mg / dL, P2 28.13 mg / dL and P3 50.65 mg / dL. HDL levels were highest in the P3 group and the lowest group was the K- group. Descriptive analysis using *the Shapiro-Wilk test* is known to all normally distributed groups with a value of (p>0.05), but has inhomogeneous data variants with Leuvene Test results (p>0.05) obtained results of 0.03, as in the following graph 5:

Analysis of the difference in average HDL levels carried out by *Tamhane Post hoc* test showed that there were significant

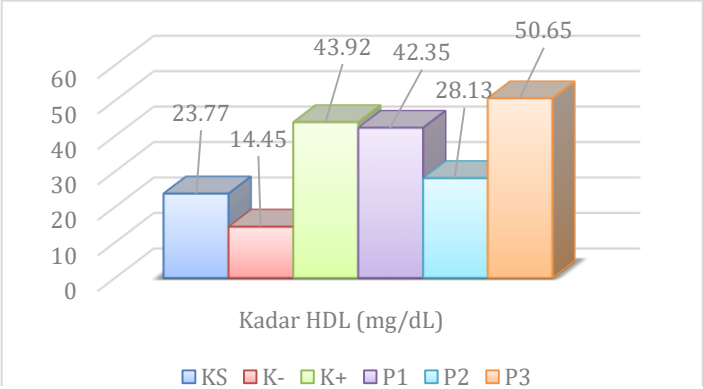

Figure 4. Average HDL levels between groups after EEKS administration

differences in the K- group with K+ 0.026, K- with P1 0.009, K- with P3 0.023 , K+ with P2 0.031 (p<0.05), It can be concluded that the P3 group with a dose of 240 mg EEKS most affected HDL levels in male rats of *the Wistar* strain induced by a high-fat diet with a significance level of 0.023. Attached to table 6 follows:

Table 5. Differences in average HDL levels in each group after EEKS administration with *Posh Hoc Tamhane test*

Group	Towards-	K+	P1	P2	P3
KS	0,45	0,22	1,00	0,99	0,98
Towards-		*0,026	*0,009	0,08	*0,002
K+			0,18	*0,031	0,30
P1				0,06	0,99
P2					0,07

Description: * Means p<0.05

IL-6 Rate Analysis Results

The average results of the IL-6 level examination were obtained in the KS group 3.07 ng / L, K- 4.02 ng / L, K + 3.35, P1 4.36 ng / L, P2 2.90 ng / L and P3 3.80 ng / L. The highest IL-6 levels in the P1 group and the lowest group were the P2 group. Descriptive analysis using the Shapiro-Wilk test is known to all normally distributed groups with a value of (p>0.05), and has a homogeneous data variance with the results of the Leuvene Test (p>0.05) obtained results of 0.068. It was concluded that the average data of IL-6 levels were normally distributed and homogeneous so that they qualified for a One way anova test to determine differences between groups.

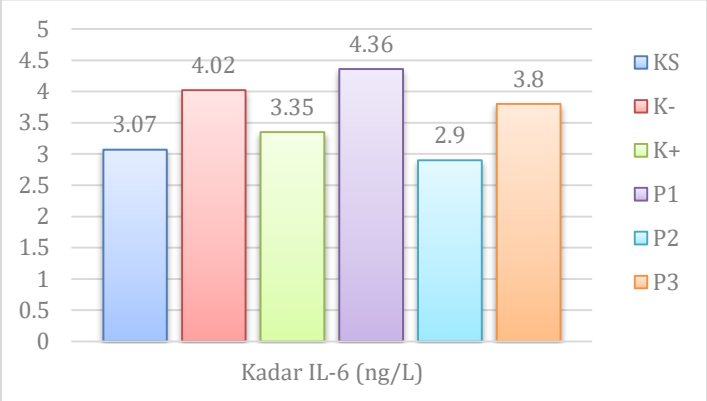

Figure.5. Graph of the average value of IL6 levels after EEKS administration in each group

The results of the one-way anova *test* obtained results of 0.032 (p < 0.05) showed there were significant differences between treatment groups, Group P2 with EEKS dose 120 mg for 14 days decreased significantly when compared to the positive group (K +) given simvastatin dose 0.18 mg / day orally, as illustrated in graph 6.

Analysis of differences in mean IL-6 levels was carried out Post hoc LSD test to determine the dose group that most affected rats with a high-fat diet intervened with EEKS, attached to the following table:

Table 6. Differences in average IL-6 levels per group after EEKS administration

Group	Towards-	K+	P1	P2	P3
KS	*0,056	0,561	*0,011	0,722	0,134
Towards-		0,171	0,485	0,26	0,654
K+			*0,043	0,351	0,350
P1				*0,005	0,256
P2					0,068

Description: * Means p<0.05

IL-6 levels of the KS group with the *LSD post hoc* test were significantly different compared to the K- group, the KS group was significantly different than the P1 group, the K+ group was significantly different than the P1 group , and the P1 group was significantly different than the P2 group. The comparison of each group with the most significant value is the P2 group of 0.005 (p < 0.05) it can be concluded that the P2 group with a dose of 120 mg has the best effect in reducing IL-6 levels.

MDA Rate Analysis Results

The average results of MDA levels were obtained in the KS group 0.13 mg / mL, K- 0.07 mg / mL, K + 0.08 mg / mL, P1 0.11 mg / mL, P2 0.09 mg / mL and P3 0.08 mg / mL. MDA levels were highest in the P1 group and the lowest group was the K- group. Descriptive analysis using the *Shapiro-Wilk* test found abnormally distributed data in the P1 group of 0.01 mg / ml and P2 0.01 mg / ml (p > 0.05), and had inhomogeneous data variants with *Leuvene Test results* (p > 0.05) obtained results of 0.03. It was concluded that the average data of MDA levels were abnormally distributed and not homogeneous so that Kruskal Wallis's non-parametric test was carried out to determine differences between groups.

The results of the Kruskal Wallis test obtained results of 0.01 (p < 0.05) showed there were significant differences between treatment groups, Group K – give n a high-fat diet without interference had the lowest value, group K + with simvastatin dose 0.18

mg / day orally with group P3 with EEKS dose 240 mg for 14 days had the same average MDA value, as illustrated in the following graph 7:

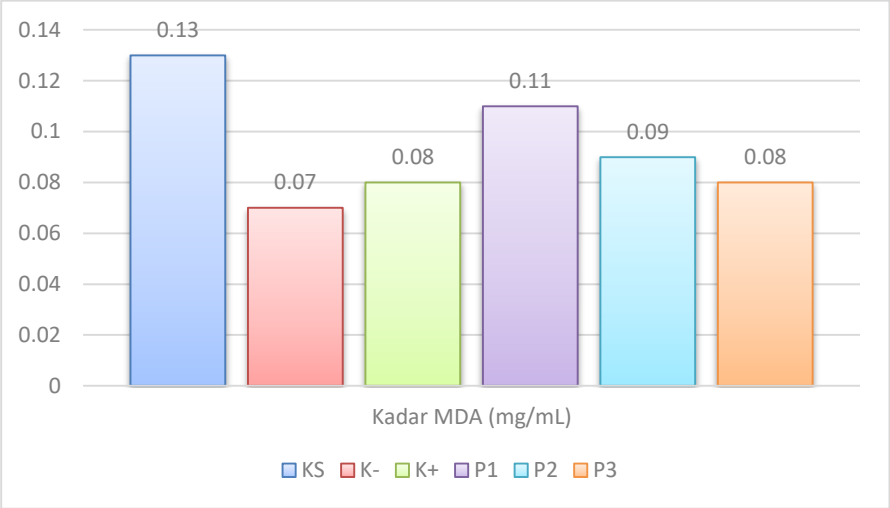

Figure 6. Graph of the average value of MDA levels after EEKS administration in each group

Analysis of differences in average MDA levels was carried out by *the Mann-Whitney* test to determine the dose group that had the most effect on rats with a high-fat diet that was intervened with salak bark extract.

The MDA levels of the KS group with the *Mann-Whitney* test were significantly different compared to the K- group with a value of 0.005 ($p<0.05$), the KS group was significantly different compared to the K+ group with a value of 0.002, the KS group was not significantly different compared to the P1 group with a value of 0.226, the KS group was significantly different compared to the P2 group with a value of 0.023, and the KS group was significantly different compared to the P3 group with a value of 0.003. It was concluded that MDA levels with the administration of salak bark ethanol extract dose of 240 mg for 14 days were most effective compared to others, as in the following table:

Table 8. Differences in mean MDA levels after EEX administration of each group with *the Mann-Whitney test*

Group	Checklists	Say
KS	Towards-	*0,005
	K+	*0,005
	P1	0,189
	P2	*0,023
	P3	*0,003

Description: * Means $p<0.05$

IV. DISCUSSION

Dyslipidemia is defined as a disorder of lipid metabolism characterized by an increase or decrease in lipid fraction levels in plasma. The main lipid fraction abnormalities are an increase in total cholesterol (K-Total), LDL cholesterol, and/or triglycerides (TG) levels and a decrease in HDL cholesterol.[14,15] Dyslipidemia that modulates the function and activity of myeloid cells, and an increase in oxidative metabolism with increased production of reactive oxygen species (ROS). As a defense mechanism, cells produce antioxidants (AOs) to prevent or limit oxidative tissue injury. Excessive ROS production can cause an imbalance between ROS and AOS leading to oxidative stress and damage, contributing to tissue injury through several mechanisms, including DNA damage, membrane lipid peroxidation, enzyme oxidation and stimulation of proinflammatory cytokines.[40] Dyslipidemia is a leading cause of heart attacks, strokes, and peripheral vascular disease. Chronic inflammation that is triggered and disrupted by the accumulation of lipids. accumulation of cells containing excess lipids within artery walls, increased formation of intracellular reactive oxygen species (ROS) play an important role in chronic inflammatory response.[25]

Dyslipidemia is a condition in which there is an increase or decrease in the fraction of lipids in the blood due to an abnormality in the metabolism of the lipid itself. The lipid fraction that experiences abnormalities is usually an increase in total cholesterol, TG, LDL levels and a decrease in HDL cholesterol.[41] In this study showed the effect of salak bark extract can reduce cholesterol, LDL,

TG levels and increase HDL levels in rats given a high-fat diet feed for 14 days. In line with research by Datu., *et al (2022) with the provision of salak fruit juice (*Salacca zalacca*)* the administration of salak fruit juice affects lipid profiles by reducing total cholesterol, triglyceride levels, and LDL levels. Giving salak juice can also reduce the weight of obese rats and reduce blood glucose levels. Research by Nuranti., *et al* (2015), reported that ethanol extract of salak fruit peel doses of 210 and 840 mg / kg of mouse weight was shown to reduce total cholesterol levels of mouse blood with the largest decrease of 23.72% (dose 840 mg / kgbb mice), but the activity was still smaller than simvastatin with a percentage reduction in total cholesterol levels of 42.08%. Unlike this study where at a dose of 120 mg EEKS given for 14 after diet treatment High fat, decreased total cholesterol levels lower than in the simvastatin group, but at a dose of 240 mg was found not lower than the simvastatin group. These results show that the optimal dose of 120 mg is better than simvastatin which needs more in-depth research.

Clinically, the most important plasma lipids are triglycerides and cholesterol. Apart from cholesterol's central role in cellular regulation and stability, it serves as a building block for steroid hormones, vitamin D, oxieol, and bile acids. Its insolubility in plasma requires its transport in spherical macromolecules called lipoproteins, which consist of a hydrophobic core, containing mainly cholesterol esters and triglycerides, and a hydrophilic layer composed of phospholipids, free cholesterol, and apolipoproteins. The main cholesterol-carrying lipoproteins are low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Imbalances in cholesterol homeostasis are triggered by increased food intake or by genetic factors resulting in the removal of cholesterol in peripheral tissues. Damage to the endothelium that causes migration of monocytes into the intima and differentiation into macrophages. Macrophage scavenger receptors mediate excessive endocytosis of modified LDL, which lacks negative feedback regulation and results in the formation of macrophage foam cells. Excessive absorption of modified LDL leads to apoptosis and cholesterol-induced inflammation. Cytokines produced by macrophages and endothelial cells stimulate smooth muscle cell proliferation. Unresolved inflammation eventually leads to plaque expansion, destabilization, and rupture.[24]

Excess intracellular cholesterol can be toxic and lead to foam cell formation and cell hardening, which in turn affects blood vessel integrity and cell signaling. Maintain a strict balance between the synthesis, absorption, and export of cholesterol, since cholesterol itself cannot be degraded in higher organisms. For cellular cholesterol depletion, cholesterol is transferred to HDL particles, which receive excess cholesterol mainly from peripheral cells and tissues to be transported back to the liver to be removed together into bile. This pathway is called reverse cholesterol transport (RCT). In contrast, circulating LDL particles, which are formed from triglyceride-rich lipoproteins after remodeling in plasma and liver, complete the transport of cholesterol to cells that require lipids. In this case, cells express higher levels of LDL-receptor (LDLR), a protein that mediates uptake of LDL particles through the classical receptor-mediated endocytosis pathway. In case of excess total body cholesterol, cholesterol will eventually accumulate in LDL particles, leading to prolonged circulation in the bloodstream. This imbalance is consequently followed by oxidation of the particle itself, leading to an increase in atherosclerotic potential and rigidity of the cell membrane. Oxidized LDL particles have been shown to induce endothelial stiffness. Atherogenic processes alter other transport processes, such as HDL transcytosis over endothelial cells, which are essential for lipid clearance in the intima. Over time, cholesterol and other lipids are deposited on the walls of blood vessels, causing plaque formation. However, the whole phenomenon begins at the cellular level when cells are faced with an excess of cholesterol.[26]

ROS, produced during mitochondrial physiological or physiopathological oxidative metabolism, reacts with various biomolecules, including lipids, carbohydrates, proteins, nucleic acids, and connective tissue macromolecules, thereby disrupting cell function. Under normal physiological conditions, there is a critical balance in the formation of oxygen free radicals and the antioxidant defense system. A decrease in oxidant/antioxidant balance triggers a situation of oxidative stress and generally results from ROS hyperproduction. Oxidative stress is known to be a component of molecular and cellular tissue damage mechanisms in a broad spectrum of human diseases. Many oxygenated compounds, especially aldehydes such as malondialdehyde (MDA) and conjugated dienes, are produced during the attack of free radicals into membrane lipoproteins and polyunsaturated fatty acids. Many studies have found that serum MDA is higher in subjects with hyperlipidemia and decreases after dietary supplementation with antioxidants[11].

Dyslipidemia causes an increase in pro-inflammatory cytokines that play a role in oxidative stress and inflammatory processes.[1] Antioxidants are an option in efforts to control dyslipidemia. The antioxidant content in salak bark extract was able to reduce MDA levels in the results of the study showed that the dose group of 240 mg EEKS was the same as the group with simvastatin dose 0.18 mg, showed the effect of EEKS that reduced inflammation so as to reduce MDA levels equaled the results of the simvastatin group, proving the antioxidant content can be an alternative choice in the treatment of dyslipidemia. Treatment and prevention of diseases with antioxidants is one of the therapeutic modalities that is not inferior to the pharmacological approach. Potent antioxidants are proven to overcome several diseases and even degenerative diseases that are not easy to handle.[8]

Lipid metabolism and peroxidation are important in the development of inflammation, which increases with some of the

complications associated with dyslipidemia.[40] IL-6 has a major role in the relationship between inflammation, obesity and cardiovascular disease. Several other findings suggest elevated interleukin (IL)-6 is used as a marker of systemic inflammation and a diagnostic marker of atherosclerotic events.[41]

V. CONCLUSION

1. Administration of salak bark ethanol extract had an effect on reducing IL-6 levels in male rats of wistar strains induced by a high-fat diet.
2. Administration of salak bark ethanol extract had an effect on reducing MDA levels in male rats of wistar strains induced by a high-fat diet.

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