Analysis Of Mangosteen Peel Ethanol Extract (Garcinia Mangostana L.) Against The Effectiveness Of Anti-Dyslipidemia In Male Rats Fed A High-Fat Diet

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ABSTRACT

Data in Indonesia (Riskesdas) in 2013 showed that there were 35.9% of the Indonesian population aged ≥ 15 years with abnormal cholesterol levels of a very high proportion of LDL (≥ 190 mg/dl), 22.9 % had HDL levels that were less than 40 mg/dl, and 11.9% with very high triglyceride levels (≥ 500 mg/dl). Mangosteen peel contains an organic compound, namely xanthones, known as anti-inflammatories and antioxidants that are strong and thought to be analgesics. Therefore, researchers are interested in exploring the effectiveness of anti-dyslipidemia from mangosteen peel extract. This study was experimental with a pre-and Post-test group-only control design approach using male Wistar rats as animals. This research was conducted in April 2022 at the Medanese Herbarium FMIPA USU, the Pharmacognosy Laboratory of the USU Faculty of Pharmacy, and the USU Pharmaceutical Pharmacology Laboratory. Mangosteen peel ethanol extract results contain several phytochemical compounds, including Alkaloids, Saponins, Flavonoids, Tannins, Steroids, and Terpenoids. Ethanol extract from mangosteen fruit peel significantly decreased total Cholesterol (P-value < 0.05), lowered triglyceride levels (P-value = 0.029), fell LDL levels (P-value < 0.05), and dropped SGOT levels (Value = 0.029) and SGPT (P-value < 0.05) compared to the control group. Mangosteen peel ethanol extract can also significantly increase HDL levels (P-value = 0.029).

Keywords: mangosteen peel, dyslipidemia, ethanol, fat.

1. INTRODUCTION

Dyslipidemia is a lipid metabolism disorder, namely an increase or decrease in lipid fractions in plasma (Indra, Tjahjono DK, and N. Setyawati, 2014). Data in Indonesia (RISKESDAS) in 2013 showed that there were 35.9% of the Indonesian population aged ⩾ 15 years with abnormal cholesterol levels of a very high proportion of LDL (⩾ 190 mg/dl), 22.9 % had HDL levels that were less than 40 mg/dl, and 11.9% with very high triglyceride levels (⩾ 500 mg/dl) (RISKESDAS, 2013). Judging by gender, women are more numerous than men, and from where they live, they live in urban areas more than in rural areas. Management of dyslipidemia, with medications, includes statins, fibrates, niacin, ezetimibe, and bile acid-binding resins (Dharmayanti, 2018). However, some reports of unwanted side effects due to fibrotic group drugs mostly require high doses and prolonged use (Arsana et al., 2015); (Shahab, 2013). So alternative treatments with side effects that may be more minimal are needed, such as herbal remedies. One of the natural ingredients that have the potential to be an alternative is mangosteen peel. Therefore, researchers are interested in exploring the effectiveness of anti-dyslipidemia from mangosteen peel extract.

2. RESEARCH METHODS

This experimental study uses a Pre-test and Post-test group-only control design approach that uses male Wistar rats as experimental animals, with as many as four male Wistar rats (Rattus norvegicus) in each treatment group. This study was conducted in November 2022; the time taken was about 6 (six) weeks, with the first week for making ethanol extract of mangosteen fruit peel, the following week for the rat acclimatization process, and four weeks was the treatment of male Wistar rats. The study was conducted at the Medanese Herbarium FMIPA USU, the Pharmacognosy Laboratory of the USU Faculty of Pharmacy, and the USU Pharmaceutical Pharmacology Laboratory.

Materials and Tools

Surgical tools, laboratory glassware, aluminum foil, blender (Miyako), porcelain cup, desiccator, incubator, object-glass, cover glass, porcelain crutch, drying cabinet, microtube, light microscope, analytical balance sheet (Vibra AJ), oral sonde, electric oven (Stork), water bath (Yenaco), tube clamp, test tube rack, rotary evaporator, centrifugation, set of water content determination tools, UV spectrophotometer (Microlet 3000), injection syringe, furnace (Nabertherm), test tubes, animal scales (Presica). The ingredients used in this study were mangosteen fruit, methanol, Aquades, Na-CMC (Sodium-Carboxyl methylcellulose), simvastatin, husk, rat food pellets, phytochemical screening reagents, and ketamine.

Making Mangosteen Peel Ethanol Extract.

Mangosteen peels simplistic was weighed 200 grams each, then extracted using the maceration technique with 96% ethanol solvent. Let stand for five days; the container must be protected from direct sunlight while stirring frequently, huskie, squeeze, and wash the pulp with enough liquid to obtain 4 L. Then the simplistic is transferred into a closed container, left in a cool place, protected from light for two days. Then this simplistic is filtered. The results were concentrated using a Rotary Evaporator tool until most of the solvent evaporated. Then, the evaporation process was continued in a water bath until a thick extract (ethanol extract of mangosteen fruit peel) was obtained.

Phytochemical Screening

In phytochemical test studies using fansworth method modifications consisting of the identification of phenols, steroids / triterpenoids, terpenoids, saponins, flavonoids, tannins and alkaloids (Widowati et al., 2017).

Testing of anti-dyslipidemia effects

1. Manufacture of 0.5% NA CMC Suspension
   A total of 0.5 grams of Na CMC is sprinkled into a mortar containing 10 mL of hot distilled water. It is allowed to stand for 15 minutes until a transparent period is obtained, ground until a gel forms and diluted with a small amount of distilled water, then poured into a 100 mL flask, plus filtered water to the limit of the mark. This suspension will be used further in the next stage as a dispersing medium in making oral suspense (Colloidal) (Mutia & Chiuman, 2019).
2. Manufacture of hypercholesterolemia feed suspension. The suspension is made by mixing 300 grams of animal fat into 100 ml of aquadest and 200 grams of poultry egg yolk into 1 ml of 0.5% Na-CMC (Harsa, 2014).
3. Mangosteen Peel Extract Suspension. A total of 1.2 grams of mangosteen peel extract was put into a mortar and a 0.5% Na CMC suspension was added little by little while grinding until homogeneous and then put into a 10 mL scalded flask. Volume is sufficient with 0.5% Na CMC suspension up to the marking line (Mutia & Chiuman, 2019).
4. Simvastatin Suspension Making. A total of 10 mg of simvastatin was grinded into a mortar until it became powder, then a 0.5% Na CMC suspension was added and then put into a 25 mL flask. Volume is sufficient with 0.5% Na CMC suspension up to the marking line (Aldahmash & El-Nagar, 2016; Fouad & Jresat, 2013).
5. Induction of Dyslipidemia in Experimental Animals. The induction process is carried out by giving a high-fat diet to experimental animals for 14 days. A high-fat diet is given by providing a suspension of high-fat feed at a dose of 15 gr/kgBB for fat animal suspension and 10 gr/kgBB for poultry egg yolk suspension. (Harsa, 2014; Untari & Pramukantoro, 2020).
6. Animal Testing. One week before the intervention, all test animals were acclimatized to the laboratory environment. After that, all Wistar rats were induced by using the hypercholesterolemic feed, except the standard group. After 14 days, test animals with total cholesterol levels ≥ 240 mg/dl were declared dyslipidemia. However, before measuring the whole cholesterol level, all rats fasted for 8 hours. The test animals were divided into six groups, each with 4 test animals. Doses of mangosteen peel ethanol extract and simvastatin as the standard group were determined based on previous research (Olayinka et al., 2014). The treatment experienced by each mouse in the group was as follows:

Table 1. Description of the Treatment of Each Group

No	Kelompok Uji	Perlakuan
1.	Normal	Test animals were not given specific treatment and were only given to eat and drink ad libitium.
2.	Control	Test animals were given 1 ml of 0.5% Na CMC suspension once a day for 14 days. Food and drinks are given ad libitum.
3.	Standard (25 mg/kgBB)	Test animals were given oral suspension simvastatin 5 ml / kgBB once a day for 14 days. Food and drinks are given ad libitum.
4.	Mangosteen Peel Ethanol Extract -	The test animals were given mangosteen peel ethanol extract at a dose of

	I (300 mg / kgBB)	2.5 ml / kgBB once a day for 14 days. Food and drinks are given ad libitum.
5.	Mangosteen Peel Ethanol Extract - II (600 mg/kgBB)	The test animals were given mangosteen peel ethanol extract at a dose of 5 ml / kgBB once a day for 14 days. Food and drinks are given ad libitum.
6.	Mangosteen Peel Ethanol Extract - III (1200 mg/kgBB)	The test animals were given mangosteen peel ethanol extract at a dose of 10 ml / kgBB once a day for 14 days. Food and drinks are given ad libitum.

Measurement of Lipid Profile Parameters

Before the blood draw, the rats were fasted at least 8 hours before the blood draw. A blood draw is carried out by direct withdrawal from the heart of mice as much as 1 ml. Put in microtubes and allow to stand ± 20 minutes. Then the blood was centrifuged at a speed of 3000 rpm for 15 minutes to get rat blood serum. The determination of lipid profile is determined by the colorimetric method. Lipid profile examination is conducted at the Health Laboratory, North Sumatra Provincial Health Office.

Measurement of Biochemical Parameters of SGOT and SGPT

A blood draw is carried out by direct withdrawal from the heart of mice as much as 1 ml. Put in microtubes and allow to stand ± 20 minutes. Then the blood was centrifuged at a speed of 3000 rpm for 15 minutes to get rat blood serum. The determination of SGOT and SGPT levels is based on an enzymatic reaction using the Dyasis® kit reagent. The procedure for determining the activity of SGOT and SGPT catalysts is based on the work procedures of Dyasis®. SGOT and SGPT examinations are conducted at the Health Laboratory, North Sumatra Provincial Health Office.

Data Analysis

The study results were analyzed descriptively (Central tendency and Dispersion) from the research data in the form of lipid profiles (LDL, HDL, Total Cholesterol, and Triglycerides). In addition, lipid profiles were analyzed with One-Way Anova if the data were normally distributed with a follow-up test in the form of a Post Hoc Tukey HSD test to see noticeable differences between treatments. However, as an alternative test, if the distributed data is abnormal, the Kruskal-Wallis test is used.

3. RESULTS AND DISCUSSION

The results of phytochemical screening on mangosteen peel ethanol extract samples can be seen in the following table. From table data 2, it can be seen that mangosteen peel ethanol extract contains several phytochemical compounds including Alkaloids, Saponins, Flavonoids, Tannins, as well as Steroids, and Terpenoids.

Table 2. Phytochemical Screening Results of Mangosteen Skin Ethanol Extract

Phytochemicals	Reagents	Result
Alkaloid	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponins	Aquadest + Alcohol 96%	-
Flavonoids	FeCl3 5%	+
	$Mg_{(s)} + HCl_{(p)}$	-
	NaOH 10%	-
	$H_2SO_{4\ (p)}$	-
Tannins	$FeCl_3$ 1%	+
Steroids and Terpenoids	Salkowsky	-
	Liberman Bouchard	+

Evaluation of anti-dyslipidemia effects

Table 3. Results of Data Normality Test with Shapiro-Wilk Test on All Research Parameters

Parameters	P-Value	Data Distribution
Weight	0.396	Normal
Total Cholesterol Before Induction	< 0.05	Abnormal
Total Cholesterol After Induction	< 0.05	Abnormal

Lipid Profile After Treatment	Total Cholesterol	0.489	Normal
	Triglycerides	0.003	Abnormal
	HDL levels	< 0.05	Abnormal
	LDL levels	0.132	Normal
SGOT levels		< 0.05	Abnormal
SGPT Levels		0.052	Normal

From the data of the table 3, it can be seen that the data on body weight, total cholesterol and LDL levels from the lipid profile after treatment, and SGPT levels have a normal data distribution, while other parameters include: total Cholesterol before and after induction, triglyceride levels, HDL levels, and abnormally distributed SGOT levels. Based on the distribution of these data, data with normal data distributions are analyzed with parametric cynics while abnormal data is analyzed with non-parametric statistics.

Table 4. Comparison of Total Cholesterol Before and After High-Fat Diet Administration in All Treatment Groups

Treatment Groups	**Total Cholesterol (mg/dL)**	
	Sebelum Induksi	**After Induction**
Normal	116.50 (110-117)	118.50 (112-121)[b]
Standard	112.00 (100-115)	211.00 (209-213)[a]
Control	115.50 (110-118)	210.50 (210-212)[b]
Mangosteen Peel Ethanol Extract -I	115.50 (110-117)	210.50 (208-214)[b]
Mangosteen Peel Ethanol Extract -II	110.50 (100-115)	210.50 (209-212)[b]
Mangosteen Peel Ethanol Extract -III	117.50 (117-120)	209.00 (208-213)[b]
P-value	**0.886**	**0.029**

The data is displayed as a Median (Range). The P value is obtained from kruskal-wallis analysis; Different superscripts in the same column show significant differences.

Table 4 shows that before being given a high-fat diet, the total Cholesterol of rats before the administration of a high-fat diet in the entire treatment group did not show a significant difference (P-value = 0.866). This suggests that the total cholesterol data of rats before being given a high-fat diet were uniform. However, total Cholesterol in the entire group of mice after administration of a high-fat diet showed a different distribution, whereas only the control group, standard ethanol extract of mangosteen peel I, II, and III showed uniform total Cholesterol.

Table 5. Comparison of Lipid Profiles across Rat Treatment Groups

Treatment Groups	**Lipid Profile**			
	Total Cholesterol *	**Triglycerides ****	**LDL***	**HDL****
Normal	134.50 ± 2.40a	98.50 (97-100)a	52.25 ± 1.71a	62.50 (61-64)a
Standard	144.50 ± 0.58b	102.50 (101-105)b	62.50 ±1.29b	61.50 (60-63)a
Control	179.25 ± 6.02c	166.50 (162-179)c	106.00 3.65c	29.50 (38-43)b
Mangosteen Peel Extract -I	168.25 ± 1.50d	133.50 (133-135)d	83.75 ±2.62d	57.50 (56-59)b
Mangosteen Peel Extract -II	163.25 ± 2.22e	120.50 (119-122)e	77.50 ± 1.29e	61.50 (61-63)a
Mangosteen Peel Extract -III	151.75 ± 0.96e	110.00 (109-112)f	68.50 ±1.29f	61.00 (60-63)a
P-Value	**< 0.05**	**0.029**	**< 0.05**	**0.029**

*The data is displayed as Mean ± SD. The P value is obtained from the One Way ANOVA analysis; **Data is displayed as Median (Range). The P value is obtained from kruskal-wallis analysis; Different superscripts in the same column show significant differences.

From the data of the table above, it can be seen that all lipid profile data in the entire treatment group showed significant differences.

a) Total Cholesterol in the entire rat treatment group showed a significant difference, this can be seen from the P-value of < 0.05. The average total Cholesterol was the lowest found in the normal group of 134.50 ± 2.40 mg / dL, followed by the standard group of 144.50 ± 0.58 mg / dL, the mangosteen peel ethanol extract group I, II, III, and the group with the highest total Cholesterol was the control group of 179.25 ± 6.02 mg / dL;
b) Triglyceride levels in the entire treatment group also showed significant differences, this can be seen from the P-value < 0.05 (P-value = 0.029). The tendency to the lowest triglyceride levels was found in the normal group,

namely, 98.50 mg / dL, followed by the standard group of 102.50 mg / dL, the mangosteen peel ethanol extract group I, II, III, and the group with the highest triglyceride levels was the control group of 166.50 mg / dL.

c) LDL levels also showed significant differences in the entire treatment group, this can be seen from the P-value of < 0.05. The lowest average LDL levels were found in the normal group of 52.25 ± 1.71 mg / dL, followed by the standard group of 62.50 ±1.29 mg / dL, the ethanol extract group of mangosteen peel I, II, III, and the group with the highest LDL levels was the control group of 106.00 ±3.65 mg / dL.

d) HDL levels also showed significant differences in all treatment groups, this can be seen from the P-value < 0.05 (P-value = 0.029). The tendency of the highest HDL levels was found in the normal group, namely, 62.50 mg / dL, followed by the standard group of 61.50 mg / dL, the mangosteen peel ethanol extract group I, II, III, and the group with the lowest HDL levels was the control group of 29.50 mg / dL.

Table 6. Comparison of SGOT and SGPT Levels in All Treatment Groups

Treatment Groups	SGOT levels (U/L)	SGPT Levels (U/L)
Normal	28.50 (27-30)[a]	47.25 ± 1.50[a]
Standard	110.50 (108-112)[b]	171.50 ± 1.29[b]
Control	168.50 (162-170)[c]	97.25 ± 1.50[c]
Mangosteen Peel Ethanol Extract -I	118.50 (118-120)[d]	100.75 ± 3.59[d]
Mangosteen Peel Ethanol Extract -II	122.50 (121-124)[e]	115.50 ± 4.51[e]
Mangosteen Peel Ethanol Extract -III	130.50 (129-132)[f]	142.50 ± 2.08[b]
P-Value	**0.029**	**< 0.05**

*The data is displayed as Mean ± SD. The P value is obtained from the One Way ANOVA analysis; **Data is displayed as Median (Range). The P value is obtained from kruskal-wallis analysis; Different superscripts in the same column show significant differences.

From the table data above, it was seen that SGOT and SGPT levels in all rat treatment groups showed significant differences, this can be seen from the P-value of < 0.05. The tendency of the highest SGOT levels was found in the control group, namely 168.50 U / L, and the lowest in the normal group, namely 28.50 U / L. Meanwhile, a similar picture was found in the SGPT level, the group with the highest SGPT levels was found in the control group, namely 171.50 U / L, and the lowest was targeted in the normal group, namely 47.25 U / L.

This study showed that mangosteen peel Ethanol extract showed significant improvement in lipid profile at the end of the study. Ethanol extract of mangosteen peel at the highest doses showed the most optimal improvement in lipid profile. This can be seen from the decrease in total Cholesterol, triglyceride, and LDL levels and an increase in HDL levels from the mangosteen skin ethanol group II and III. However, this improvement in lipid profile in the Mangosteen-III Fruit Peel Ethanol Extract rat group did not exceed the gains shown in the standard group.

The anti-dyslipidemia effect of ethanol extract from mangosteen peel can be related to the content of various phytochemicals in the mangosteen fruit. Some studies have shown the potential of phytochemicals as anti-dyslipidemia. For example, Polyphenol content can cause down-regulation of pro-inflammatory cells' signal modulations such as nuclear factor-κB, activated protein-1, and mitogen-activated protein kinase through inhibition from a cascade of arachidonic acids and eicosanoids derivatives. Another mechanism that allows the anti-dyslipidemia effect of polyphenol compounds is the regulation of intestinal microbiota. The polyphenol compounds in the usu will interact with the gut microbiota, thereby increasing beneficial metabolite products such as short-chain free fatty acids and use microbes such as Akkermansia municiphilia sp. to restore inflammatory conditions in the intestines, improving intestinal permeability and sensitivity of insulin. Furthermore, this improvement to the intestinal microbiota protects the gut-liver axis, lowering the lipid profile in the body (Sun et al., 2018).

Other studies discussing the anti-dyslipidemia effects of ethanol in mangosteen peel are still limited. However, Dharmayanti (2018), who conducted a study on the Effect of Mangosteen Peel Ethanol Extract (Garcinia Mangostana. L) on LDL Levels in NIDDM Type Mice, reported that mangosteen peel extracts affected reducing LDL in NIDDM-type mice (Dharmayanti, 2018). Saturated fatty acids have an essential role in the synthesis of LDL cholesterol. Therefore, the diagnosis of dyslipidemia can be established based on an increase in LDL in plasma. Xanthones found in mangosteen peel are antioxidant, antidiabetic, anticancer, anti-inflammatory, hepatoprotective, immunomodulation, aromatase inhibitor, antibacterial, also other functional; Mangosteen peel (Garcinia mangostana. L) is beneficial for health because it contains anthocyanins, tannins, phenol/polyphenol compounds, epicatechin, and xanthones (Supiyanti et al., 2010).

In addition, ethanol extract from mangosteen peel significantly lowered SGOT and SGPT levels compared to the control group. This decrease in SGOT and SGPT levels is related to improving Non-Alcoholic Fatty Liver Disease (NAFLD). Several studies have shown that NAFLD is a risk factor for the formation of arteriosclerosis. This is

because NAFLD causes dysfunction of the vascular endothelium. Thong and Quynh (2021) report that both SGOT and SGPT correlate with the occurrence of NAFLD, but the use of SGOT and SGPT separately may show errors in confirming mild NAFLD. In severe CASES of NAFLD, SGOT will increase slightly; in milder cases, SGOT levels can be found in average amounts. Therefore, unilateral use of SGOT and SGPT can allow errors in confirming mild degree NAFLD (Thong and Quynh, 2021). In this study, SGOT and SGPT levels in the rats who received mangosteen peel ethanol extract were lower than the SGOT and SGPT levels of the control group. This suggests that mangosteen peel ethanol extract can protect liver tissue from NAFLD compared to the group that did not receive mangosteen peel ethanol extract. However, the possibility of mild NAFLD in the group of mice that got mangosteen peel ethanol extract could not be ruled out.

4. CONCLUSIONS

The conclusions that can be drawn from the results of this study are ethanol extract of mangosteen fruit peel significantly decreased total Cholesterol (P-value < 0.05), lowered triglyceride levels (P-value = 0.029), lowered LDL levels (P-value < 0.05) and lowered SGOT levels (Value = 0.029) and SGPT (P value < 0.05) compared to the control group. In addition, Mangosteen peel ethanol extract can also significantly increase HDL levels (P-value = 0.029).

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