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The Effect of Ethanol Extract of Starfruit Leaves (Averrhoa Bilimbi L.) on Total Cholesterol Levels in White Wistar Male Rats Induced by High-Fat Feed

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Indonesia has high biodiversity and great potential as a source of traditional medicine. Lipid metabolism disorders, particularly increased total cholesterol levels, are a major risk factor for cardiovascular disease, the prevalence of which continues to increase due to high-fat consumption patterns and lifestyle changes. The starfruit plant (Averrhoa bilimbi L.) is known to contain secondary metabolites such as flavonoids, saponins, tannins, and alkaloids that have the potential to play a role in lowering total cholesterol levels. This study aims to determine the effect of administering ethanol extract of starfruit leaves (Averrhoa bilimbi L.) on total cholesterol levels in male Wistar rats induced by a high-fat diet. This study is an experimental study with a post-test control group design. A total of 30 male Wistar rats were divided into six groups, namely normal control (KN), negative control (K-), positive control (K+), and three treatment groups given starfruit leaf extract at a dose of 120 mg/KgBW (P1), 240 mg/KgBW (P2), and 480 mg/KgBW (P3). The rats were induced with a high-fat diet for 14 days, then given treatment for 14 days. Total cholesterol levels were examined on days 8, 22, and 35. Data were analyzed using the Shapiro-Wilk test, Levene's test, One-Way ANOVA, and Games-Howell follow-up test. The results showed that high-fat feed induction successfully increased total cholesterol levels in the negative control group. Administration of starfruit leaf extract at all doses significantly reduced total cholesterol levels compared to the negative control group ($p<0.05$). The 240 mg/kgBW dose (P2) showed the most effective reduction in total cholesterol levels with a mean value of 104.80 ± 3.11 mg/dL, comparable to the positive control group (simvastatin). Ethanol extract of starfruit (Averrhoa bilimbi L.) leaves effectively reduced total cholesterol levels in male Wistar rats fed a high-fat diet, with the most effective dose being 240 mg/kgBW. This extract has the potential to be developed as an alternative to traditional antihyperlipidemic drugs.
Keywords: Ethanol Extract, Starfruit Leaves, Cholesterol, Rats

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1. Introduction

Indonesia is known as an archipelagic nation with a very high level of biodiversity, including a wealth of flora and fauna. Various studies indicate that Indonesia has hundreds of plant families, many of which have the potential to be used as medicinal plants. This diversity makes Indonesia one of the countries with important natural resources for the development of traditional and herbal medicines.

The World Health Organization (WHO) recommends the use of traditional medicines as part of health maintenance efforts and the prevention and control of degenerative diseases, including lipid metabolism disorders such as elevated total cholesterol levels. The use of natural plant-based ingredients is considered to have great potential because they contain various bioactive compounds that can affect lipid metabolism and have long been used empirically by the community.

Lipid metabolism disorders, particularly elevated total cholesterol levels, are a major risk factor for cardiovascular disease, the prevalence of which continues to increase globally. A high-fat, low-fiber diet,

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and lack of physical activity are contributing factors to elevated blood cholesterol levels. In Indonesia, changes in modern lifestyles and diets have contributed to the increasing prevalence of lipid disorders, necessitating the need for safe and effective alternative therapies, including the use of traditional medicines based on local medicinal plants (Ministry of Health of the Republic of Indonesia, 2018).

Total cholesterol is the total amount of cholesterol in the blood, consisting of LDL, HDL, and VLDL, which play a crucial role in the formation of cell membranes, steroid hormones, and bile acids. However, high saturated fat intake and an unbalanced diet can lead to increased total blood cholesterol levels and disrupt lipid metabolism (Rosdiana & Wibowo, 2019). Elevated total cholesterol generally does not cause typical symptoms in the early stages, but over the long term, it can lead to complaints such as fatigue and decreased stamina due to impaired blood circulation (Sari & Nugraha, 2021). Hypercholesterolemia is a condition in which blood cholesterol levels are high. This is what happened in a 2018 study, Health Research.

In general, elevated total blood cholesterol levels do not always cause typical symptoms in the early stages. However, under certain conditions, symptoms such as fatigue, decreased stamina, discomfort, and impaired blood circulation due to lipid accumulation in the blood vessels can occur. Total cholesterol levels are assessed through laboratory blood tests using enzymatic methods. Elevated total cholesterol levels are considered when the value is ≥200 mg/dL. Total cholesterol reflects the accumulation of lipoprotein fractions, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL), and is therefore often used as an early indicator of lipid metabolism disorders. The main factors influencing total cholesterol increases include high-fat diet consumption, excessive saturated fat intake, and lipid metabolism imbalances. Therefore, high-fat diet-induced animal models are widely used to evaluate the effectiveness of natural ingredients in lowering total cholesterol levels (Grundy et al., 2018; Rosdiana & Nugraha, 2020). The starfruit plant (Averrhoa bilimbi L.) is a plant with potential for development as a traditional medicine due to its known content of secondary metabolites such as flavonoids, saponins, tannins, and alkaloids. These compounds are reported to have antioxidant activity that plays a role in regulating lipid metabolism, potentially lowering total cholesterol levels. Therefore, research on the effect of ethanol extract of starfruit leaves on total cholesterol levels in male Wistar rats induced by a high-fat diet is important as a scientific basis for the development of traditional antihyperlipidemic medicines (Putri et al., 2020; Sari & Handayani, 2021).

The increasing problems of lipid metabolism due to high-fat consumption patterns have prompted the development of safer cholesterol-lowering agents, one of which is the use of medicinal plants. Traditional medicines based on natural ingredients have long been used by the community as alternative therapies based on empirical experience and their abundant availability in the surrounding environment. The use of medicinal plants is considered to have advantages in the form of relatively fewer side effects, affordable costs, and can be used as a supporting therapy in maintaining balanced cholesterol levels in the blood (Putri & Rahman, 2020; Sari et al., 2021).

2. Methods

The cholesterol test method used a high-fat diet. The subjects were 30 male white Wistar rats, divided into six groups of five rats each. This study took place in the Laboratory of the Faculty of Medicine, Prima Indonesia University, Medan, using primary data collection methods. This involved testing starfruit leaf extract (Averrhoa bilimbi L.) on the total cholesterol levels of male white rats (Rattus norvegicus) induced by a high-fat diet.

Equipment and Materials

The equipment used in this study included a blender, rotary evaporator, beaker glass, stirring rod, mortar and pestle, dropper, test tube, dropper plate, filter paper, funnel, measuring cylinder, Erlenmeyer flask, analytical balance, animal scale, animal cage, syringe, oral probe, test tube, test tube rack, cotton swab, stopwatch, handscoon, mask, blood glucose meter, and test strips.

The materials used in this study were starfruit leaves (Averrhoa bilimbi L.) from male white Wistar rats (Rattus norvegiccus), high-fat feed, PA (Pro Analytical) ethanol, simvastatin, 1% CMC, chloroform, sulfuric acid, 2N HCl, Mayer's reagent, Dragendorf, Mg metal, concentrated HCl, methanol, 1% ferric chloride, 3% ferric chloride, distilled water, anhydrous acetic acid, and concentrated sulfuric acid.

Research Procedure

Before conducting the study, the tools and materials were sterilized. Then, samples of starfruit leaves (Averrhoa bilimbi L.) were collected and processed. The leaves were not too young or too old. They were cleaned from their branches by washing them under running water and drying them in the sun. Once dry, the leaves were ground using a blender. Next, the Belimbing Wuluh Leaf Extract was made using the maceration method, 500 grams of belimbing wuluh leaf powder was put into a maceration container and 5000 ml of 96% ethanol solvent was added, then closed and wrapped and left for 3 days and stirred 1x24 hours for 10 minutes every day then filtered to separate the residue and extract, using filter paper. The entire macerate was left to stand and then evaporated using a rotary evaporator at a temperature of 69°C-70°C and concentrated until a thick extract of belimbing wuluh leaves was obtained. Next, the phytochemical screening test of belimbing wuluh leaves (Averrhoa bilimbi L.) was carried out, namely the test of alkaloids, flavonoids, phenolics, saponins, terpenoids and steroids. Preparation of experimental animals, as many as 30 rats were acclimatized for 7 days, divided into 6 groups of rats and each group consisted of 5 rats. In this study, the dose of starfruit leaf extract (Averrhoa bilimbi L.) administered to the experimental animals was divided into three planned doses: 120 mg/kgBW, 240 mg/kgBW, and 480 mg/kgBW. This study used primary data obtained from the blood LDL levels of rats fed a high-fat diet for 14 days. The rats were fed a mixture of high-fat feed or cooked beef tallow with butter from day 8 to day 21. Cholesterol levels were then checked on day 8 before being fed the high-fat diet. Cholesterol levels were checked on day 22 to day 35 before treatment (simvastatin and extract). Simvastatin was administered orally daily during treatment from day 22 to day 35.

On day 35, cholesterol levels were checked after 14 days of simvastatin and both the drug and extract. It should be noted that on days 8, 22, and 35, serum tests were carried out. Blood was taken from the eyes of the mice and then centrifuged to separate the plasma and serum which would be checked in the Kesda lab.

3. Results and Discussion

Starfruit Leaf Extraction (Averrhoa bilimbi L.)

The first step in starfruit leaf extraction is to collect the crude drug. The leaves used are neither too young nor too old. The leaves are cleaned and then dried indoors, away from direct sunlight, for two weeks. Afterward, they are blended into a dry crude drug powder and weighed. 500 grams of the dried crude drug is obtained. Next, maceration is performed with 5L of ethanol, left for three days, with one repetition (remaceration). After 24 hours, the extract is stirred for 10 minutes and filtered using filter paper to obtain a liquid extract of the reed stem. After obtaining the liquid extract, the leaves are then evaporated in a rotary evaporator and then in a water bath to obtain a thick extract of the reed stem, amounting to 29 grams.

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Phytochemical Screening Test of Starfruit Leaves (Averrhoa bilimbi L.)

Phytochemical screening tests are one of the initial stages of phytochemical research, which aim to provide an overview of the types of compounds contained in the plant being studied.

Table 1. Phytochemical Test Results of Stem Extract (Saccharum Spontaneum L.)

No	Secondary metabolite compounds	Results
1.	Alkaloids	+ (Positive)
2.	Flavonoids	+ (Positive)
3.	Tannins	+ (Positive)
4.	Saponins	+ (Positive)
5.	Triterpenoids	+ (Positive)

No mice died after induction of high-fat feeding or during treatment, therefore, no mice met the exclusion criteria. Because the Shapiro-Wilk normality test in this study yielded normal data ($p>0.05$) and the Levene's homogeneity test yielded heterogeneous data ($p<0.05$), the data were then subjected to a one-way ANOVA and Games-Howell post hoc test. There were six research groups: group KN (normal control) consisted of rats fed a standard diet, distilled water, and no treatment; group K- (negative control) consisted of rats fed a high-fat diet and no treatment intervention; group K+ (positive control) consisted of rats fed a high-fat diet and given simvastatin 0.18% mg/200gBW/day; group P1 (treatment 1) consisted of rats fed a high-fat diet and given starfruit extract at a dose of 120 mg/200gBW/day; group P2 (treatment 2) consisted of rats fed a high-fat diet and given starfruit leaf extract at a dose of 240 mg/200gBW/day; and group P3 (treatment 3) consisted of rats fed a high-fat diet and given starfruit leaf extract at a dose of 480 mg/200gBW/day.

Table 1. Results of the Shapiro-Wilk Normality Test

Group	Observation Time	Sig. Value
KN	Day 1	-
	Day 5	-
	Day 10	-
	Day 15	-
	Day 20	-
	Day 25	-
	Day 30	-
K-	Day 1	0,154
	Day 5	0,824
	Day 10	0,861
	Day 15	0,727
	Day 20	0,391
	Day 25	0,724
	Day 30	0,206
K+	Day 1	0,940
	Day 5	0,382
	Day 10	0,687
	Day 15	0,849
	Day 20	0,617
	Day 25	0,325
	Day 30	0,063
P1	Day 1	0,254

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Group	Observation Time	Sig. Value
	Day 5	0,994
	Day 10	0,700
	Day 15	0,780
	Day 20	0,935
	Day 25	0,907
	Day 30	0,758
P2	Day 1	0,254
	Day 5	0,195
	Day 10	0,638
	Day 15	0,809
	Day 20	0,537
	Day 25	0,560
	Day 30	0,420
P3	Day 1	0,421
	Day 5	0,184
	Day 10	0,476
	Day 15	0,708
	Day 20	0,455
	Day 25	0,452
	Day 30	0,318

KN: Normal Group, K+: Positive Group, K-: Negative Group, P1: Treatment 1, P2: Treatment 2, P3: Treatment 3.

a. Normality Test

The Shapiro-Wilk test for normality yielded a normal data distribution. Based on the results of the Shapiro-Wilk test, the results for each group had a significance value greater than (p>0.05), thus concluding that the data were normally distributed. In other words, the assumption of normality was met.

Table 2. Homogeneity Test and ANOVA

Observation Time	Levene Test	One-Way ANOVA
Day 1	0,049	0,003
Day 5	0,032	0,000
Day 10	0,016	0,016
Day 15	0,051	0,000
Day 20	0,004	0,000
Day 25	0,004	0,000
Day 30	0,000	0,000

b. Homogenity Test

The homogeneity test of data variance was conducted using the Levene Test (Levene Test Homogeneity of Variance). Based on the analysis results, observations on day 1, day 5, day 10, day 20, day 25, and day 30 obtained a significance value of less than 0.05 (p<0.05), thus concluding that the data variance in these observations was not homogeneous. Meanwhile, on day 15 obtained a significant value of p>0.05, so it can be concluded that the data in the homogeneity test on day 15 is declared homogeneous.

c. One-Way ANOVA Test

Based on the results of the One-Way Anova test analysis, a significance value of less than 0.05 ($p<0.05$) was obtained at all observation times on all days, so it can be concluded that there is a significant difference in cholesterol levels between treatment groups at each observation time.

Table 3. Results of the LSD Post Hoc Test

Observation Time	Treatment	KN	K+	K-	KP1	KP2	KP3
Day 1	KN		0,040	0,047	0,062	0,134	0,113
	K+	0,040		0,981	0,264	0,664	0,980
	K-	0,047	0,981		0,479	0,930	1,000
	KP1	0,62	0,264	0,479		0,969	0,702
	KP2	0,134	0,664	0,930	0,969		0,974
	KP3	0,113	0,980	1,000	0,702	0,974	
Day 5	KN		0,006	0,001	0,000	0,003	0,008
	K+	0,006		0,188	0,922	0,960	0,849
	K-	0,001	0,188		0,208	0,033	0,027
	KP1	0,000	0,922	0,208		0,313	0,233
	KP2	0,003	0,960	0,033	0,313		0,997
	KP3	0,008	0,849	0,027	0,233	0,997	
Day 10	KN		0,000	0,002	0,002	0,003	0,005
	K+	0,000		0,004	0,319	0,051	0,028
	K-	0,002	0,004		0,183	0,791	0,985
	KP1	0,002	0,319	0,183		0,787	0,518
	KP2	0,003	0,051	0,791	0,787		0,993
	KP3	0,005	0,028	0,985	0,518	0,993	
Day 15	KN		0,000	0,000	0,001	0,000	0,000
	K+	0,000		0,780	0,805	0,743	0,889
	K-	0,000	0,780		1,000	1,000	1,000
	KP1	0,001	0,805	1,000		1,000	0,999
	KP2	0,000	0,743	1,000	1,000		0,999
	KP3	0,000	0,889	1,000	0,999	0,999	
Day 20	KN		0,000	0,004	0,001	0,001	0,000
	K+	0,000		0,000	0,000	0,000	0,000
	K-	0,004	0,000		0,001	0,001	0,005
	KP1	0,001	0,000	0,001		0,246	0,003
	KP2	0,001	0,000	0,001	0,246		0,022
	KP3	0,000	0,000	0,005	0,006	0,022	
Day 25	KN		0,000	0,018	0,004	0,002	0,009
	K+	0,000		0,000	0,003	0,001	0,000
	K-	0,018	0,000		0,006	0,002	0,054
	KP1	0,004	0,003	0,006		0,443	0,014
	KP2	0,002	0,001	0,002	0,443		0,011
	KP3	0,009	0,000	0,054	0,014	0,011	
Day 30	KN		0,000	0,479	0,035	0,010	0,116
	K+	0,000		0,000	0,006	0,000	0,000
	K-	0,479	0,000		0,043	0,009	0,814
	KP1	0,035	0,006	0,043		0,486	0,057
	KP2	0,010	0,000	0,009	0,486		0,019

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Observation Time	Treatment	KN	K+	K-	KP1	KP2	KP3
	KP3	0,116	0,000	0,814	0,057	0,019	

d. Post Hoc Games-Howell

The next step was to conduct a Games-Howell post hoc test to determine which group differed from the others. The initial hypothesis (H0) proposed in this study was that there was no significant difference in cholesterol reduction between groups. The alternative hypothesis (Ha) was that there was a significant difference in cholesterol reduction between groups. Conclusions were drawn based on the proposed hypotheses by comparing the obtained significance value with the alpha value determined by the researcher. In this study, the alpha value used was 0.05 (5%). Hypothesis H0 is accepted if the significance value obtained from the analysis results is greater than 0.05 ($p>0.05$), and hypothesis Ha is rejected. Otherwise ($p>0.05$), H0 is rejected and Ha is accepted.

Table 4. Average Data

Time	KN	K-	K+	P1	P2	P3	p-value
Day 1	100,00 ± 0,00	108,00 ± 3,54	106,60 ± 3,05	108,00 ± 3,54	104,80 ± 3,11	106,40 ± 3,91	0,003
Day 5	100,00 ± 0,00	132,80 ± 8,47	145,80 ± 6,83	136,60 ± 3,36	129,00 ± 6,52	127,00 ± 7,48	0,000
Day 10	100,00 ± 0,00	231,60 ± 16,33	176,00 ± 14,37	205,80 ± 19,92	189,80 ± 19,51	183,00 ± 20,31	0,016
Day 15	100,00 ± 0,00	235,80 ± 13,55	223,80 ± 15,64	223,40 ± 17,70	223,40 ± 15,04	226,60 ± 14,22	0,000
Day 20	100,00 ± 0,00	235,80 ± 9,03	120,60 ± 4,72	174,80 ± 11,56	158,60 ± 9,13	136,20 ± 3,90	0,000
Day 25	100,00 ± 0,00	222,20 ± 16,25	110,00 ± 3,54	162,40 ± 14,62	147,40 ± 8,76	123,00 ± 6,60	0,000
Day 30	100,00 ± 0,00	215,20 ± 5,26	103,80 ± 4,32	146,00 ± 19,49	128,00 ± 8,40	107,20 ± 4,44	0,000

The K- group had the highest average cholesterol levels (108.00 ± 3.54), while the P3 group had the lowest (106.40 ± 3.91). The K+ group had an average cholesterol level of 106.60 ± 3.05, which was almost comparable to the P3 group. Table 4 shows the results of cholesterol level measurements in mice before and after induction. Each group consisted of five mice. The table shows that cholesterol levels in mice increased after induction.

The K- group had a higher cholesterol level than the K+ group, with a value of 108.00 ± 3.54. In this group, the test animals were induced with a high-fat diet without medication or starfruit leaf extract. This group can be used as a comparison to observe the impact of a high-fat diet on total cholesterol levels. The results in the K- group were significantly higher than those in the KN group, which received no medication or treatment at all. This indicates that high-fat feeding successfully increased total cholesterol levels.

Meanwhile, in P1, with starfruit leaf extract administered at a dose of 120 mg/200gBW/day, the P1 group's cholesterol level decreased slightly, but not significantly, nearly equivalent to the P2 group's cholesterol level of 104.80 at a dose of 240mg/200gBW/day. However, a slight increase occurred in the P3 group, with a value of 106.40 at a dose of 480mg/200gBW/day. This is likely due to the doubling of the dose, which could be due to the mice's immune response. At this dose, instead of lowering cholesterol levels, the mice instead caused mild metabolic stress in the livers. This study demonstrates that administering starfruit

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leaf extract (Averrhoa bilimbi L.) at a dose of 120 mg/dL to the P2 group effectively reduced total cholesterol levels.

4. Conclusion

In this study, starfruit leaf extract (Averrhoa bilimbi L.) was shown to reduce cholesterol levels in rats fed a high-fat diet. The results of the analysis in group P2 were almost equivalent to group P3, and P2 was the most effective dose for reducing total cholesterol levels, with cholesterol levels of 104.80 ± 3.11. For future research, it would be advisable to conduct toxicity tests and conduct studies with varying doses to identify the most effective dose in reducing total cholesterol levels.

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