E-ISSN: 2528-410X

RESEARCH ARTICLES

The Effect of Mangrove Leaf Extract (*Rhizophora apiculata*) on Blood Cholesterol Levels of White Mice (*Mus musculus*) Induced by Egg Yolk

Putri Ridha Yuliansyah[1], Nurfadly[2], Emni Purwoningsih[3], Humairah Medina Liza Lubis[4]

[1] Faculty of Medicine and Health Sciences , Universitas Muhammadiyah Sumatera Utara, Medan, Jalan Gedung Arce No 53 Medan 20217, Indonesia
[2] Department of Parasitology, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Medan, Jalan Gedung Arce No 53 Medan 20217, Indonesia
[3] Department of Biochemistry, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Medan, Jalan Gedung Arce No 53 Medan 20217, Indonesia
[4] Department of Pathology Anatomy, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Medan, Jalan Gedung Arce No 53 Medan 20217, Indonesia

Corresponding Email: putriridhaaa@gmail.com

Abstract: Cholesterol is the primary sterol in the human body, produced by the liver. While essential, excessive cholesterol can accumulate as plaques in blood vessels. Rhizophora apiculata contains secondary metabolites such as flavonoids, tannins, alkaloids, saponins, and terpenoids, which are believed to influence HDL and LDL levels. This study aims to investigate the effect of Rhizophora apiculata leaf extract on HDL and LDL levels in male white mice (Mus musculus) induced with egg yolk. This true experimental study applied a post-test with a control group design. A total of 36 white mice were divided into six groups, consisting of negative, positive, and treatment groups. Mice were acclimatised for one week, induced with quail egg yolk, and administered Rhizophora apiculata leaf extract for 30 days. Blood HDL and LDL levels were then measured and analysed using One-way ANOVA. The Shapiro-Wilk and Levene's tests showed p-values >0.05. The One-way ANOVA indicated significant differences in HDL and LDL levels between groups ($p<0.05$). LSD post hoc tests showed treatment groups P1, P2, and P3 differed significantly from the negative control. Rhizophora apiculata leaf extract affects HDL and LDL levels in male white mice induced by egg yolk.

Keywords: HDL, LDL, *Rhizophora apiculata*

INTRODUCTION

Cholesterol is the main sterol circulating in the human body. It is a structural component of cell membranes and lipoproteins produced by the liver. Cholesterol has a very important function for the body. However, if cholesterol levels exceed the normal limit, cholesterol will

E-ISSN: 2528-410X

accumulate in the blood vessels and then form plaque that can block blood vessels.[1] Plaque causes the lumen of the artery to narrow, resulting in a lack of blood flow entering the heart muscle, which is known as atherosclerosis.[2] Atherosclerosis is a cardiovascular disease that is one of the main problems in monitoring health problems in developed and developing countries.[3]

Cholesterol is classified into HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), and TG (Triglycerides). LDL carries cholesterol throughout the body through the arteries, so if an LDL level is too high, it will accumulate on the walls of the arteries. HDL is responsible for returning excess cholesterol to the liver to be removed from the body. So, the higher the HDL level, the better it is for the body. Conversely, excessive LDL cholesterol, triglycerides, and total cholesterol levels can harm health. High cholesterol is a combination of high levels of total cholesterol, triglycerides, LDL, and low levels of HDL. [2,3]

The prevalence of cholesterolemia in the world is around 45%, and in Southeast Asia, it is around 30%. In Indonesia, cholesterol prevalence is quite high, reaching 28%. If this cholesterolemia is treated too late, it will endanger health and can even cause death.[4,5]

In addition to living a healthy lifestyle, several types of drugs can help lower cholesterolemia. Statins are one of the drugs used to lower LDL cholesterol and triglycerides. They can increase HDL cholesterol.[6] This drug works by inhibiting the enzyme needed to form cholesterol, so that the cholesterol levels that the body will produce will be reduced. Although very useful for lowering cholesterol levels, there are several side effects due to the use of this statin drug, such as constipation, nausea, headache, stuffy nose, sneezing, sore throat and in most people, simvastatin can cause forgetfulness or confusion.[7] In addition, the effects of drug interactions can occur if used with certain drugs, such as increasing the risk of muscle dysfunction (myopathy), including rhabdomyolysis and the risk of bleeding, impaired kidney and liver function.[7]

Herbal ingredients can be used as an alternative to lower cholesterol levels because they are easy to find, safe, affordable, easy to cultivate, and economical, one of which is by using mangrove leaves.[8] Mangrove leaves (*Rhizopora apiculata*) are plants people use for everyday life, and young mangrove leaves are widely used as complementary vegetables for food. In addition, coastal communities also use mangrove leaves as traditional medicines, where this mangrove plant contains various active ingredients beneficial from the roots, stems, leaves, and others.[8] *Rhizopora apiculata* leaves are widely used as traditional medicines, such as antidiarrhea, slimming, and antiemetics. *Rhizopora apicu*lata leaves also contain several compounds of the alkaloid, flavonoid, phenol, saponin, steroid, and terpenoid groups.[9]

E-ISSN: 2528-410X

Previous studies concluded that ethanol extract of *Rhizophora apiculata* stems contains *lyoniresinol-3α-O-β-arabinopyranoside*, *lyoniresinol-3α-O-β-rhamnoside*, and *afzelechin-3-O-L-rhamno-pyranoside,* which have antioxidant activity as tested by DPPH (*1,1-diphenyl-2-picrylhydrazyl*) and ABTS (*2,2-azinobis-3-Ethylbenzothiazoline-6-Sulfonic Acid*) methods.[10] Based on the results of the study, the content of compounds in *Rhizopora apiculata* leaves, such as flavonoids, tannins, and phenolics, are strong sources of antioxidants because they can donate protons to neutralize free radicals and administration of 95% ethanol extract of *Rhizophora apiculata* leaves can prevent an increase in total cholesterol levels in white rats (*Rattus norvegicus*) induced by a high-fat diet. The effective dose of 95% ethanol extract of *Rhizophora apiculata* leaves to prevent an increase in total cholesterol levels in Sprague Dawley White Rats (*Rattus norvegicus*) is 28 mg/kgbw, and triglycerides 14 mg/kgbw.[11] In another study, *Rhizophora apiculata* leaf extract can prevent an increase in total cholesterol and triglyceride levels, with the highest decrease in *Malondialdehyde* (MDA) at a dose of 56 mg/kgbw/day. [12]

Previous research aimed to study the effect of *Rhizophora apiculata* leaf extract on total cholesterol levels in the blood, but its effect on LDL and HDL levels was not explained, so the author was interested in conducting a study to see the impact of *Rhizophora apiculata* leaf extract on HDL and LDL levels in white mice (*Mus musculus*) induced by egg yolk.

METHODS

This study uses the True Experiment method, with the selected research design being a Post-test with a Control Group Design, which was carried out in September-December 2023 at the Laboratory of the Faculty of Medicine, University of Muhammadiyah North Sumatra.

The sample was male white mice that met the inclusion and exclusion criteria. Quota Sampling is carried out using a simple random sampling technique. The sample size in this experimental study was determined using the sample size formula, which was calculated using the Federer formula. The required sample size was obtained as many as four mice per group; each group added two reserve mice, then multiplied by six groups; the total number of samples was 36 mice. 1 kg of *Rhizopora apiculata* leaves is washed clean, then dried by air to be crushed when cut into small pieces, then ground using a blender. The ground *Rhizopora apiculata* leaf powder is macerated with 96% ethanol solvent with a ratio of 1 5 or 100 grams of powder with 500mL of 96% ethanol until all metabolites are extracted; the sample will be stored for 3 x 24 hours and filtered using filter paper, after being filtered it will be evaporated using a Rotary vacuum Evaporator to obtain a liquid extract, and weighed to calculate the immersion. After receiving the liquid extract, a phytochemical test is carried out to

E-ISSN: 2528-410X

determine what compounds are contained in each extract qualitatively. The compounds tested were alkaloids, flavonoids, triterpenoids, saponins, tannins, and phenolics. The doses to be given to White Mice (*Mus musculus*) are 28 mg/kgbw/day, 14 mg/kgbw/day, and 7 mg/kgbw/day.

The mice were then acclimatized for seven days and divided into six groups, namely KN given standard feed, K- given standard feed + 0.5 ml egg yolk; K+ given standard feed + 0.5 ml egg yolk + 0.5ml simvastatin/20 mg/kgbw/day; P1 given 0.5 ml egg yolk + 28 mg/kgbw/day *Rhizopora apiculata* leaf extract; P2 given 0.5 ml egg yolk + 7 mg/kgbw/day *Rhizopora apiculata* leaf extract; and P3 given 0.5 ml egg yolk + 7 mg/kgBW/day *Rhizopora apiculata* leaf extract. The treatment was given for 30 days for each group.

Blood samples were taken from the hearts of mice through surgery, as much as 1 ml and put into an EDTA tube. Then, the blood will be incubated for 30 minutes at room temperature and centrifuged for 15 minutes at 3000 rpm. The plasma is taken, and then the serum HDL and LDL levels are examined using the Thermo Scientific Multiskan GO spectrophotometry tool at the University of North Sumatra Laboratory. The data obtained were analysed using the SPSS statistical application with the Shapiro-Wilk Normality Test, Levene's Homogeneity Test, One-way ANOVA Parametric Test, and LSD post hoc test. This study has received approval from the Ethics Committee of the Faculty of Medicine, University of Muhammadiyah North Sumatra, with the number 1084 / KEPK / FKUMSU / 2023.

RESULT

Phytochemical tests in this study were conducted to see the secondary metabolite content in *Rhizophora apiculata* leaf extract. The results of the phytochemical test can be seen in Table 1.

Table 1. Phytochemical tests

Compound	+/-
Alkanoid	+
Flavonoid	+
Terpenoid	-
Steroid	+
Saponin	+
Tanin	+
Fenolik	+

Description: (+) = Contained; (-) = Not contained.

When examining HDL levels, the lowest average HDL levels were found in the K—group and the highest in the P1 group, while the highest LDL levels were in the K- group and the lowest in the P1 group. The average HDL and LDL levels data from each mouse can be seen in Table 2.

Table 2. Average HDL and LDL levels

	HDL Levels (mean±SD) mg/dL	LDL Levels (mean±SD) mg/dL
KN	27,125±1,8987	57,1725±7,4748
K+	45,5±3,0387	24,945±2,6682
K-	18,375±2,0988	85,835±9,5556

E-ISSN: 2528-410X

	HDL Levels (mean±SD) mg/dL	LDL Levels (mean±SD) mg/dL
P1	83,5075±5,2932	24,1175±1,8276
P2	63,1825±10,6542	29,9725±3,9023
P3	44,0125±6,9785	40,4225±7,5834

In the research data, a normality test was carried out using the Shapiro-Wilk test and a data homogeneity test using the

	KN	K+	K-	P1	P2	P3
KN	-	0,000*	0,029*	0,000*	0,000*	0,000*
K+	0,000*	-	0,000*	0,000*	0,000*	0,355
K-	0,029*	0,000*	-	0,000*	0,000*	0,000*
P1	0,000*	0,000*	0,000*	-	0,000*	0,000*
P2	0,000*	0,000*	0,000*	0,000*	-	0,000*
P3	0,000*	0,355	0,000*	0,000*	0,000*	-

Levene test; a P value> 0.05 was obtained, which means that the data distribution is normal and homogeneous, so a one-way ANOVA analysis test was carried out. The One-way ANOVA test determines the differences between research groups after treatment. From the results of the one-way ANOVA test, it is known that there are differences between these research groups, as indicated by a p-value <0.05.

Table 3. Comparison of average HDL levels.

Group	Average HDL Levels (mg/dL)	Significancy Levels
KN	27,125±1,8987	
K+	45,5±3,0387	
K-	18,375±2,0988	< 0,001
P1	83,5075±5,2932	
P2	63,1825±10,6542	
P3	44,0125±6,9785	

Table 4. Comparison of average LDL levels.

Group	Average LDL Levels (mg/dL)	Significancy
KN	57,1725±7,4748	
K+	24,945±2,6682	
K-	85,835±9,5556	< 0,001
P1	24,1175±1,8276	
P2	29,9725±3,9023	

Determination of the effective dose of *Rhizopora apiculata* extract can be done using an additional post hoc LSD test. Based on the post hoc LSD test, there was an insignificant difference (p-value > 0.05) in HDL between K+ and P3.

Table 5. Effective Dose of *Rhizopora apiculata* extract for reducing average HDL levels.

Description: * = p-value < 0.05

Based on the post-hoc LSD test, there was no significant difference (p-value > 0.05) in LDL between K+ P1 and P2.

Table 6. Effective Dose of *Rhizopora apiculata* extract for reducing average LDL levels.

	KN	K+	K-	P1	P2	P3
KN	-	0,000*	0,000*	0,000*	0,000*	0,001*
K+	0,000*	-	0,000	0,854	0,266	0,000*
K-	0,002*	0,000*	-	0,000*	0,000*	0,000*
P1	0,000*	0,852	0,000*	-	0,198	0,002*
P2	0,000*	0,266	0,000*	0,198	-	0,028*
P3	0,001*	0,002*	0,000*	0,002*	0,028*	-

Description:
*** = p-value < 0.05 (meaningful).**

DISCUSSION

Mangrove leaves contain alkaloids, flavonoids, triterpenoids, steroids, saponins, and tannins, each of which has been proven

E-ISSN: 2528-410X

to be a strong anti-cholesterolemic compound due to its ability to donate protons to stabilise free radicals.[35] Based on previous research, alkaloids in mangrove leaf extract can increase fat excretion through defecation by inhibiting the activity of the pancreatic lipase enzyme.[35] Then Tannin will reduce the number of cholesterol levels by slowing down the HMG-CoA reductase enzyme, which works together with mucosal proteins and epithelial cells in the intestine to block fat absorption.[35] Steroids can work by inhibiting cholesterol synthesis by inhibiting the HMG-CoA reductase enzyme and reducing fat absorption, and LDL (Low-Density Lipoprotein) is also inhibited. Saponins will also bind cholesterol with bile acids to lower cholesterol levels.[35] While Flavonoids will work as inhibitors of the HMG-CoA reductase enzyme, which plays a role in synthesising cholesterol, if the enzyme is inhibited, cholesterol levels can decrease.[37] Flavonoids will also increase the production of apo-A1 (Apolipoprotein), increasing HDL cholesterol.[35]

Based on the research that has been done, some results show changes in the average levels of HDL (High-Density Lipoprotein) and LDL (Low-Density Lipoprotein) after giving quail egg yolks for 30 days. The average HDL level in the KN group (Normal Group) was 27.12 mg/dL, which was a significant difference from the K- group (Negative Group) at 18.37 mg/dL, so that it can prove that the high-fat feed given can lower HDL levels. The average LDL level in the KN group was 57.17 mg/dL, significantly different from the K- group of 85.835 mg/dL, thus proving that the high-fat feed could increase LDL levels. The decrease in HDL and increase in blood LDL levels in this study were in line with several other studies that stated that giving quail egg yolks could cause cholesterolemia.[38] The decrease in HDL levels and the increase in LDL levels in this study were as expected, given that giving quail egg yolks could cause cholesterolemia, as in previous studies, which stated that cholesterol levels from quail eggs were 3,650 mg/100g higher than cholesterol levels from other foods. [35]

After giving mangrove leaf extract at a dose of 28 mg/kg bb/day, 14 mg/kg bb/day, and 7 mg/kg bb/day for 30 days, it can increase HDL levels and decrease LDL levels. This proves that the anti-cholesterol compounds in *Rhizophora apiculata* leaf extract can increase HDL levels and decrease LDL levels. This is based on previous research on the effect of ethanol extract from *Rhizophora apiculata* leaves on total cholesterol in *Rattus norvegicus* induced by a high-fat diet.[35]

The effectiveness of the anti-cholesterolemia of the three doses of mangrove leaf extract was compared with the K+ group (Positive Group). It can be seen from the statistical method in the LSD post hoc test (Table 4.5). The results of HDL levels showed no significant difference (p-value> 0.05) between K+ and P3. This can statistically show that mangrove leaf extract with a dose of 7 mg/kg bb/day can have the same anti-cholesterolemic effect as statin

E-ISSN: 2528-410X

drugs to reduce hypercholesterolemia. However, compared to K+ with groups P1 (Treatment 1) and P2 (Treatment 2), there is a significant difference where 14 and 28 mg/kg bb/day can increase HDL levels better. So, the effective dose of mangrove leaf extract that will prevent increased HDL levels is 7 mg/kg bb/day.

In the Post-hoc LSD test, which has the effect of anti-cholesterolemic activity of mangrove leaf extract on LDL levels (Table 4.6), the results showed no significant difference (p-value>0.05) between the K+ group and the P2 group. This statistically shows that mangrove leaf extract with a dose of 14 mg/kg bb/day has the same anti-cholesterolemic effect as statin drugs to reduce hypercholesterolemia. However, if K+ is compared with group P1, there is a significant difference, where the 28 mg/kg bb/day dose group can lower LDL levels better. Therefore, the effective dose of mangrove leaf extract that can prevent a decrease in LDL levels is 14 mg/kg bw /day.

CONCLUSION

Based on the results of the research that has been done, it can be concluded that mangrove leaf extract (*Rhizopora apiculata*) affects blood HDL and LDL levels in white mice (*Mus musculus*) induced by egg yolk. The effective dose of *Rhizopora apiculata* leaf extract on HDL (High-density lipoprotein) levels in this study was 7 mg/kg bb/day, and the effective dose of *Rhizopora apiculata* leaf extract on LDL (Low-density lipoprotein) levels in this study was 14 mg/kg bb/day.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to the Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, for providing facilities and support for this research. Special thanks to the laboratory staff for their assistance in conducting the experiments, and to all colleagues who contributed valuable insights during the study process.

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