Global Medical and Health Communication

Online submission: https://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v12i3.14070

GMHC. 2024;12(3):212–217
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

Effect of *Ketapang* Leaf Extract on HDL Levels of *Rattus norvegicus* Induced by High-fat Foods

Nurfadly Nurfadly,[1] Muhammad Fajar,[1] Isra Thristy,[2] Yenita Yenita[3]

[1]Department of Parasitology, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, Indonesia, [2]Department of Biochemistry, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, Indonesia, [3]Department of Pharmacology, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, Indonesia

Abstract

High-density lipoprotein (HDL) functions to transport cholesterol from the blood vessel endothelium to the liver and excreted through the digestive tract so that it does not cause dyslipidemia, which is a risk factor for cardiovascular disease. Current treatment for dyslipidemia uses long-term statin drugs, which can cause various side effects, so herbal alternatives such as *ketapang* leaves (*Terminalia catappa* L.), which contain flavonoids and have the effect of increasing HDL levels, needed to be evaluated to achieve that reason. This study aims to evaluate whether *ketapang* leaf extract has an effect on increasing blood HDL levels. This research used experimental animals with a pretest and a posttest with a control group design. It was conducted at the Biochemistry Laboratory and Laboratory Animal Management Unit, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, from September to December 2023. This study used Wistar strain male white rats (*Rattus norvegicus*) that were induced on a high-fat diet, divided into five groups: negative control, positive control (given simvastatin), treatment 1 (given 21 mg/kgBW *ketapang* leaf extract), treatment 2 (given 42 mg/kgBW *ketapang* leaf extract) and treatment 3 (given 84 mg/kgBW *ketapang* leaf extract). The study results showed a significant difference ($p<0.05$) in the average HDL levels before and after treatment in the positive control, treatment 2, and therapy three groups. Thus, the study concluded that *ketapang* leaf extract affected increasing HDL levels of male white rats (*Rattus norvegicus*).

Keywords: HDL, high-fat diet, *ketapang* leaf extract, *Rattus norvegicus*

Introduction

Cholesterol is vital in cell growth, produces sex hormones and vitamin D, and controls nerve and brain functions. However, excess cholesterol in the blood can cause dyslipidemia and increase the risk of cardiovascular disease. Cholesterol cannot dissolve in the blood, so lipoproteins are needed to distribute cholesterol throughout the body.[1] Dyslipidemia is a condition of abnormal lipid levels in the blood circulation, decreased levels of high-density lipoprotein (HDL), increased levels of cholesterol, low-density lipoprotein (LDL), and triglyceride levels.[2] One type of cholesterol that has a good role for the body is HDL, which is responsible for transporting cholesterol from the blood vessel endothelium so that it does not accumulate cholesterol in the blood vessel endothelium, which is then taken to the liver and excreted through the digestive tract.[3] Increasing blood cholesterol levels will impact the risk of atherosclerosis; the presence of HDL will clean blood vessels from cholesterol. Besides transporting cholesterol, HDL also widens blood vessels due to increased nitric oxide production.[4] There were no symptoms associated with low HDL levels, but they did increase the risk of cardiovascular disease.[5] Cardiovascular disease accounts for 30% of all deaths in the world; this is due to uncontrolled and untreated dyslipidemia.[6,7]

Current treatment for dyslipidemia uses statin drugs. One group of commonly used statins is simvastatin. Simvastatin works by inhibiting the HMG-CoA enzyme, which plays a role in cholesterol synthesis in the liver, so that cholesterol production is reduced.[8] Although it is beneficial for lowering cholesterol levels, there are side effects due to the use of this class of statin

Received: 9 August 2024; Revised: 31 October 2024; Accepted: 12 December 2024; Published: 22 December 2024

Correspondence: Dr. Nurfadly, M.KT. Department of Parasitology, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara. Jln. Gedung Arca No. 53, Medan 20117, Sumatera Utara, Indonesia. E-mail: nurfadly@umsu.ac.id

drugs, such as obstipation, nausea, headaches, stuffy nose, sneezing, and sore throat; in some people, it can cause forgetfulness or confusion. In addition, drug interaction effects can occur if used with certain drugs, such as increasing the risk of muscle disorders (myopathy), rhabdomyolysis, the risk of bleeding, and impaired liver and kidney function.[9,10] So, alternative medicine is needed for treatment, such as herbal treatment, which is expected to minimize side effects and provide good benefits for the body.

Ketapang (*Terminalia catappa* L.) is known as a tropical almond belonging to the family Combretaceae. They are grown mainly for shade and ornamental purposes and are primarily found in yards. The research results show that *ketapang* leaves contain flavonoids, saponins, and tannins. Flavonoids are one of the polyphenolic compounds that have antihypercholesterolemic effects; polyphenols can inhibit the work of HMG-CoA reductase so that cholesterol synthesis in the body decreases, and flavonoids can also increase HDL levels by increasing apolipoprotein one, which is the essential ingredient for forming HDL.[11,12]

Previous research shows that *ketapang* leaves have a role in reducing total cholesterol levels. It is known that the highest average reduction in cholesterol levels in male mice (*Mus musculus* L.) was found in *ketapang* leaf extract at 8 mg/kg body weight. The group given 16 mg *ketapang* leaf extract per kg body weight showed almost the same results as the positive control group (simvastatin).[13] This study aims to evaluate whether *ketapang* leaf extract has an effect on increasing blood HDL levels of male Wistar white rats (*Rattus norvegicus*) induced by a high-fat diet.

Methods

The research used an experimental study method using experimental animals with a pretest and a posttest with a control group design. The research was conducted at the Biochemistry Laboratory and Laboratory Animal Management Unit, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, from September to December 2023. The population of this study was adult male Wistar white rats (*Rattus norvegicus*) aged >3 months, weighing 100–150 grams, healthy and active, and had never been used in research. In this study, the sample was divided into five groups, and the number of samples per group was calculated using the Federer formula; the number of samples per group was five rats. The hypercholesterolemic rats were created by giving them a high-fat diet using quail egg yolks.

The research was carried out for twenty-seven days. The rats acclimatized for seven days to adapt to the environment. On the eighth day, they were separated into groups and given egg yolk for eight days, and on the fourteenth day, the LDL levels were checked before treatment; on the fifteenth to the twenty-fifth day they were given *ketapang* leaf extract with various doses, namely group P1 was given 21 mg/kgBW, P2 was given 42 mg/kgBW and P3 was given 84 mg/kgBW, on the twenty-sixth day, HDL levels were checked after treatment (Figure). This research was registered with the Health Research Ethics Committee, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, with registration number 1097/KEPK/FKUMSU/2023. Statistical analysis was done using SPSS, normality, and homogeneity tests before comparing the differences between groups using one-way ANOVA followed by post hoc LSD.

Results

The average HDL levels of male Wistar white rats after being given egg yolk for 7 days and before being given *ketapang* leaf extract were as follows: negative control group was 33 mg/dl, positive control group was 27.20 mg/dl, treatment group 1 was 27.60 mg/dl, treatment group 2 was 25.80 mg/dl and treatment group 3 was 25 mg/dl. The average HDL levels of male Wistar white rats after being given *ketapang* leaf extract were as follows: negative control was 34.40 mg/dl, positive control was 40.80 mg/dl, treatment group 1 was 30 mg/dl, treatment group 2 was 32 mg/dl and treatment group 3 was 39.20 mg/dl.

In Table 1, it can be seen that there is a significant difference in the average HDL before and after treatment ($p<0.05$) in the positive control group; there is an increase in the average HDL level after administration of simvastatin. Likewise, the average HDL before and after treatment in groups K2 and K3 increased the average HDL levels after administering *ketapang* leaf extract.

Table 2 shows no significant difference

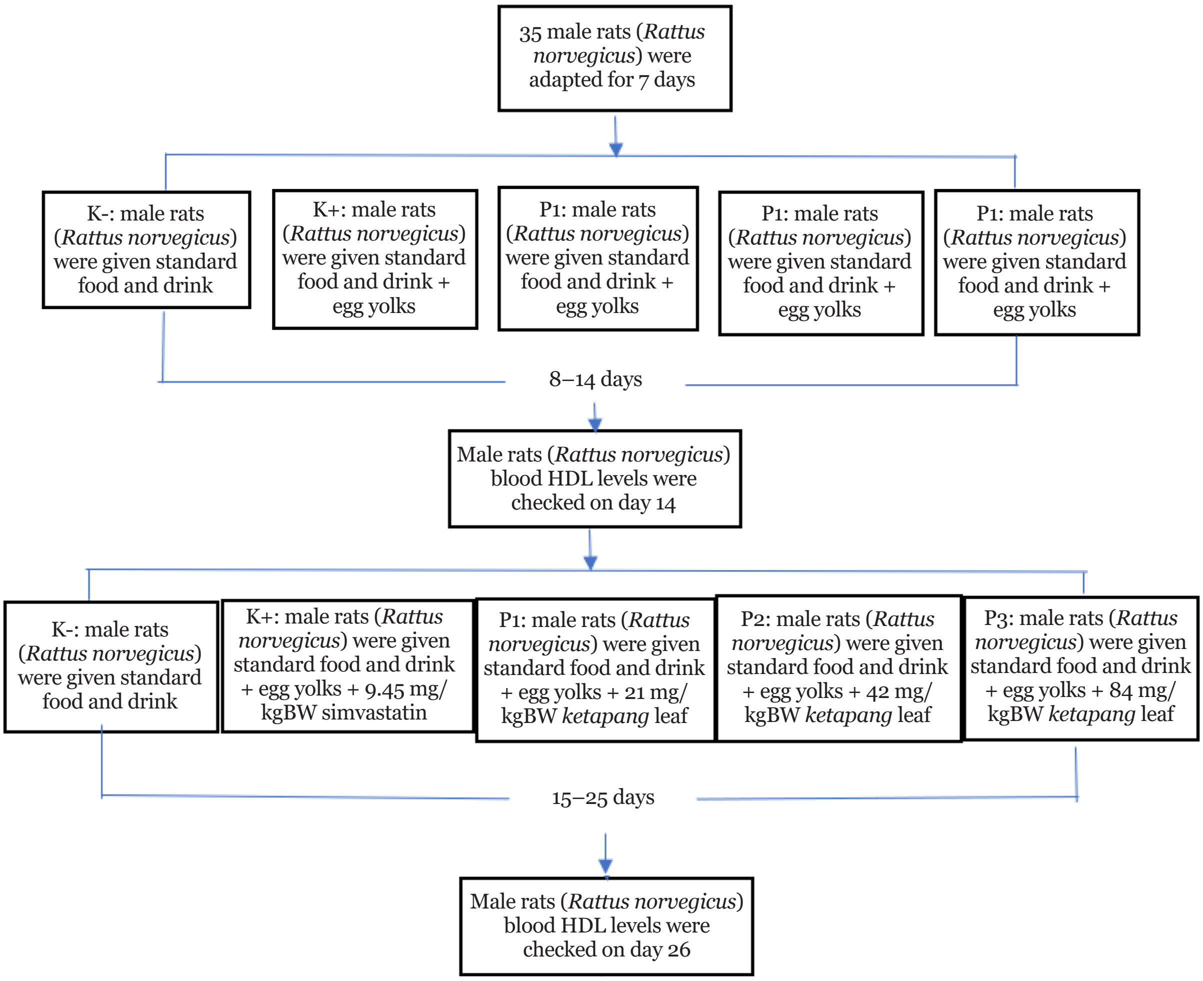

Figure Research Flow

(p>0.05) between the average HDL levels in the K+ and P3 groups, so the dose of *ketapang* leaf extract given to the P3 group can be taken as an effective dose.

Discussion

In this study, all groups of male Wistar white rats, except the negative control group, were given high-fat food in quail egg yolks to create a hypercholesterolemia model of rats. Quail eggs have the second highest cholesterol content after duck eggs and have twice as high cholesterol levels (844 mg/dl) as chicken eggs (423 mg/dl).[14,15] After seven days of giving rats high-fat food, there was a decrease in the average HDL blood levels in all

Table 1 Difference in Average HDL Levels before and after Treatment

Groups	Before Treatment Mean±SD (mg/dl)	After Treatment Mean±SD (mg/dl)	p
Negative control (K-)	33.00±4.06	34.40±2.96	0.500
Positive control (K+)	27.20±2.77	40.80±1.92	0.000
Treatment 1 (P1)	27.60±3.04	30.00±3.87	0.250
Treatment 2 (P2)	25.80±4.49	32.00±2.54	0.004
Treatment 3 (P3)	25.00±3.67	39.20±2.14	0.000

Table 2 Comparison of Average HDL Levels between Treatment Groups

	K-	K+	P1	P2	P3
K-					
K+	0.003				
P1	0.039	<0.001			
P2	0.250	<0.001	0.337		
P3	0.025	0.441*	<0.001	0.001	

Note: LSD post hoc test, *effective dose

groups compared to the negative control group. High-fat foods cause a decrease in HDL levels by increasing lipid absorption so that the amount of lipid in peripheral cells will increase, followed by an increase in reverse cholesterol transport activity and the inability to compensate for and decrease HDL levels.[16] Hypercholesterolemia causes a decrease in HDL levels because cholesterol tends to affect the balance of total cholesterol in the blood, which can affect the level of HDL.[17,18] Hypercholesterol can also change the activity of the lipoprotein lipase enzyme, which plays a role in the formation and metabolism of HDL, thereby causing decreased production or increased degradation of HDL.[16]

In this study, simvastatin was used as a positive control because simvastatin is the most effective drug that lowers cholesterol levels. It works by inhibiting cholesterol synthesis in the liver by inhibiting the HMG-CoA reductase enzyme.[19,20]

The study showed the effect of giving *ketapang* leaf extracton the HDL levels of male white Wistar rats induced by a high-fat diet. There was an increase in HDL levels in each treatment group after being given *ketapang* leaf extract. The average blood HDL levels of white male Wistar rats in the treatment groups with doses of 21 mg/kgBW, 42 mg/kgBW, and 84 mg/kgBW after being given *ketapang* leaf extract increased compared to the average HDL levels before being given it. This is in line with previous research, which shows that *ketapang* leaves affect the increase in total cholesterol and LDL levels and decrease HDL levels.[13]

Based on the results of phytochemical tests, the secondary metabolite chemical compound group in *ketapang* leaf simplex contains flavonoids, tannins, saponins, and alkaloids.[21] Flavonoids inhibit cholesterol synthesis, cholesterol esterification synthesis, and inhibit HMG-CoA reductase activity.[22] Flavonoids show the potential to improve HDL function through their well-documented effects on cellular antioxidant status and inflammation.[12] Following previous research, organic celery extract containing flavonoids increases HDL levels in white mice fed high-fat diets.[23] Flavonoid compounds also have a mechanism for increasing HDL levels by increasing the release of cholesterol from macrophages, increasing the expression of ATP-binding cassette, and increasing apolipoprotein A1, the primary material for the formation of HDL.[24] Tannin extract can reduce the accumulation of cholesterol in the blood, accelerate the removal of cholesterol through feces, and does not occur through the enterohepatic cycle.[25] Saponin was able to inhibit dietary fat absorption by inhibiting pancreatic lipase activity, its ability to prevent hypercholesterolemia, and increase HDL.[26] Alkaloids have been demonstrated to regulate lipid metabolism by enhancing energy metabolism, promoting lipid phagocytosis, and inhibiting adipocyte proliferation and differentiation.[27]

The effectiveness of *ketapang* leaf extract in increasing HDL levels can be seen statistically in the LSD post hoc test (Table 2). The HDL levels of the group given *ketapang* leaf extract with various concentrations (P1, P2, P3) were compared with the positive control group, namely the group given simvastatin. The HDL levels of groups P1 and P2 showed significant differences with the positive control group, while group P3 did not show significant differences with the control group. This indicates that 84 mg/kgBW *ketapang* leaf extract has the same effect as simvastatin.

Conclusion

This research concludes that *ketapang* leaf extract could increase the HDL levels of male white Wistar rats (*Rattus norvegicus*) induced by a high-fat diet.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

We thank the Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Medan, Indonesia, for the support.

References

1. Corallo R. Cholesterol. In: Tugman B, Baxter S, Wu Y, editors. A guy's guide: what every man needs to know about their health [e-book]. Montreal: Pressbooks; 2021 [cited 2024 June 12]. Available from: https://pressbooks.pub/btugman2021/chapter/cholesterol.
2. Aswania GM, Yasmin AAADA. Dislipidemia sebagai prediktor kejadian kardiovaskular mayor pada pasien infark miokard akut. EJ Medika Udayana. 2020;9(11):91–100.
3. Apriyanto DR, Frisqila C. Perbandingan efektivitas ekstrak dan fermentasi buah naga merah terhadap penurunan kadar kolesterol low density lipoprotein (LDL) pada tikus putih yang dibuat hiperkolesterolemia. Tunas Medika J Kedokteran Kesehat. 2016;3(3):1–5.
4. Rafsanjani MS, Asriati A, Kholidha AN, Alifariki LO. Hubungan kadar high density lipoprotein (HDL) dengan kejadian hipertensi. J Prof Medika. 2019;13(2):74–81.
5. Zhao X, Wang D, Qin L. Lipid profile and prognosis in patients with coronary heart disease: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord. 2021;21(1):69.
6. Braun A. Does low HDL cholesterol cause symptoms? [Internet]. New York: Verywell Health; 2024 [cited 2024 July 10]. Available from: https://www.verywellhealth.com/low-hdl-symptoms-signs-symptoms-and-complications-5188643.
7. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. Nat Rev Cardiol. 2021; 18(10):689–700.
8. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: review of safety and potential side effects. Acta Cardiol Sin. 2016;32(6):631–9.
9. Abu Mellal A, Hussain N, Said AS. The clinical significance of statins-macrolides interaction: comprehensive review of in vivo studies, case reports, and population studies. Ther Clin Risk Manag. 2019;15:921–36.
10. Valentovic M. Simvastatin. In: Enna SJ, Bylund DB, editors. xPharm: the comprehensive pharmacology reference. Philadelphia: Elsevier; 2007. p. 1–4.
11. Zeka K, Ruparelia K, Arroo RRJ, Budriesi R, Micucci M. Flavonoids and their metabolites: prevention in cardiovascular diseases and diabetes. Diseases. 2017;5(3):19.
12. Millar CL, Duclos Q, Blesso CN. Effects of dietary flavonoids on reverse cholesterol transport, HDL metabolism, and HDL function. Adv Nutr. 2017;8(2):226–39.
13. Maharadingga M, Pahriyani A, Arista D. Uji aktivitas ekstrak etanol 70% daun ketapang (*Terminalia catappa* L.) pada hamster Syrian jantan hiperglikemia dan hiperkolesterolemia dengan parameter pengukuran kolesterol total dan LDL. Lumbung Farmasi. 2021;2(2):80–8.
14. Waluyo J, Wahyuni D. The effect of ketapang leaf extracts (*Terminalia catappa* L.) on the cholesterol levels of male mice (*Mus musculus* L.) hypercholesterolemia. IJAERS. 2017;4(7):45–9.
15. Thomas KS, Jagatheesan PNR, Reetha TL, Rajendran D. Nutrient composition of Japanese quail eggs. IJSET. 2016;5(3):1293–5.
16. Moffatt RJ, Stamford B. Lipid metabolism and health. Boca Raton: CRC Press; 2006.
17. Nurfianti A, Tribudi YA. Kadar malondialdehid (MDA) dan kolesterol pada telur puyuh yang diberi pakan tambahan tepung pegagan (*Centella asiatica*). JTP. 2016;17(3):187–94.
18. Guo J, Chen S, Zhang Y, Liu J, Jiang L, Hu L, et al. Cholesterol metabolism: physiological regulation and diseases. MedComm. 2024; 5(2):e476.
19. Pappan N, Awosika AO, Rehman A. Dyslipidemia. [Updated 2024 Mar 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 July 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560891.
20. Feingold KR. Cholesterol lowering drugs. [Updated 2024 Feb 12]. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.

com, Inc.; 2000 [cited 2024 July 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395573.
21. Herli MA, Wardaniati I. Skrining fitokimia ekstrak etanol dan fraksi daun ketapang yang tumbuh di sekitar Univ. Abdurrab, Pekanbaru. JOPS. 2019;2(2):38–42.
22. Baskaran G, Salvamani S, Ahmad SA, Shaharuddin NA, Pattiram PD, Shukor MY. HMG-CoA reductase inhibitory activity and phytocomponent investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia. Drug Des Devel Ther. 2015;9:509–17.
23. Syafitri S, Ayu PR, Wijaya SM. Pengaruh pemberian ekstrak seledri (*Apium graveolens* L.) organik terhadap kadar high density lipoprotein (HDL) tikus putih (*Rattus novergicus*) galur Sprague Dawley yang diberi pakan tinggi lemak. J Kesehat Tambusai. 2022;3(1):88–95.
24. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther. 2022;7(1):265.
25. Yao J, Chen P, Apraku A, Zhang G, Huang Z, Hua X. Hydrolysable tannin supplementation alters digestibility and utilization of dietary protein, lipid, and carbohydrate in grass carp (*Ctenopharyngodon idellus*). Front Nutr. 2019;6:183.
26. Marrelli M, Conforti F, Araniti F, Statti GA. Effects of saponins on lipid metabolism: a review of potential health benefits in the treatment of obesity. Molecules. 2016; 21(10):1404.
27. Ma Z, Wang S, Miao W, Zhang Z, Yu L, Liu S, et al. The roles of natural alkaloids and polyphenols in lipid metabolism: therapeutic implications and potential targets in metabolic diseases. Curr Med Chem. 2023;30(32):3649–67.