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Ethanolic Extract of *Tamarindus indica* Leaves Lowers Total Cholesterol, Triglycerides, and HDL but Without Affecting LDL in Hyperlipidemic Rats

Tri Susiloningsih [1)], Wulan Christijanti*[2)], Aditya Marianti[3)], Nugrahaningsih WH[4)]
[1,2,3,4)] Biology Study Program, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang. Kampus FMIPA UNNES Jalan Raya Sekaran-Gunungpati Semarang
*Corresponding author: wulan.christijanti@mail.unnes.ac.id

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Abstract *- Hyperlipidaemia is a condition of increased lipid levels, especially cholesterol, triglycerides, LDL and an abnormal decrease in HDL in the blood. Tamarind leaves contain flavonoid and quercetin compounds that have the ability as antihyperlipidemia agents. The purpose of this study was to examine the effect of tamarind leaf ethanol extract on the lipid profile of hyperlipidaemia rats. Samples of 16 male Wistar rats were divided into 4 groups; Control group and the tamarind leaf ethanol extract treatment group was divided into 3, namely P1 350 mg/kgBB, P2 500 mg/kgBB, and P3 650 mg/kgBB. All rats were given lard 3 mL/head/day for 2 weeks. In weeks 3 and 4, rats were given extract of Tamarindus indica leaves and 2 hours interval was given lard. The data obtained were statistically analysed using one-way ANOVA and the Least Significant Difference (LSD) test at the 95% confidence level. In this study, HDL levels decreased along with reductions in total cholesterol and triglycerides, but had no effect in reducing LDL levels. Reduced cholesterol synthesis limits substrate availability for HDL formation, resulting in proportional decreases in HDL-C. The conclusion of this study is that tamarind leaf ethanol extract has an effect in reducing lipid profile levels.*

Keywords: *Tamarind leaves, Tamarindus indica, Hyperlipidemia, Cholesterol, Triglycerides.*

INTRODUCTION

Hyperlipidemia is a condition of increased lipid levels, especially cholesterol, triglycerides, LDL and an abnormal decrease in HDL (Hu et al., 2021). Abnormal increase in lipid content in the blood and will be stored in the walls of arteries, liver, and other organs. This acts as the forerunner of many dangerous health diseases such as stroke, atherosclerosis and continues to coronary heart disease (Nalla et al., 2023). According to a report from WHO, 2022 hyperlipidemia is the main cause in both developed and developing countries as a risk factor for coronary heart disease and stroke. Globally, one third of coronary heart disease is caused by high lipid levels, estimated to cause 2.6 million deaths (4.5% of the total) and 29.7 million Disability Adjusted Life Years (DALYS) or 2% of the total DAYLS. Cholesterol levels can increase due to food intake derived from animal fats such as egg yolks, shrimp, beef, lard, poultry, cheese, and butter (Danawati, 2022). Cholesterol is insoluble in blood so it requires a carrier in the form of lipoprotein, therefore cholesterol is divided into two, namely LDL and HDL (Naru, Febriani, & Syukriah, 2023). Low-density lipoprotein (LDL) is considered the main carrier of cholesterol; at least two-thirds of circulating cholesterol is in the form of LDL in peripheral tissues. HDL molecules are thought to do the opposite. High-density lipoprotein HDL takes excess LDL cholesterol and returns it to the liver for excretion (Huff, Boyd, & Jialal, 2024).

Triglyceride levels can increase due to excess fat intake, carbohydrates, obesity, smoking, hereditary factors and others (Khasanah, Setiyobroto, & Kurdanti Khasanah, 2017). Fat intake also directly affects triglyceride levels, the higher the fat consumption, the higher the synthesis of triacylglycerol in the liver and the higher the triglyceride levels in the blood (Putri, Angraini, &

Kurniawan, 2017). The pathophysiology of hyperlipidemia is related to the metabolism and transport of lipids in the body. The total amount of cholesterol from the small intestine to the body also depends mainly on the efficiency of intestinal cholesterol absorption and the amount of cholesterol consumed each day. Cholesterol absorbed from the small intestine can regulate cholesterol synthesis in the liver, depending on the amount of daily food intake. High cholesterol biosynthesis in the liver causes more very low-density lipoprotein (VLDL) to be secreted into the plasma, thereby increasing the concentration of total plasma and LDL cholesterol (Wang et al., 2017). High blood triglyceride levels are caused by high VLDL levels (Loaloka & Pantaleon, 2020).

Indonesia is known as the world's center of medicinal plants and has natural potential that can be used as an alternative medicine to treat hyperlipidemia (Iqbal *et al.*, 2022). One of the plants that has the potential as a medicinal plant is tamarind (*Tamarindus indica*). Ethanol extract of tamarind leaves contains phenolics, flavonoids, saponins, and alkaloids (Buanasari, Warlan, & Chyntia, 2018). Tamarind leaves contain flavonoid derivative compounds, namely quercetin (Yunita & Khodijah, 2020).

Flavonoids are known to be able to lower blood cholesterol levels by inhibiting cholesterol biosynthesis by preventing the formation of mevalonic acid so that cholesterol cannot be synthesized by the body (Maghfiroh, Hariani, & Khaleyla, 2021). Flavonoids increase the activity of the lipoprotein lipase enzyme which will increase the hydrolysis of triglycerides into fatty acids and glycerol to be released into the blood vessels (Veronica, Bambang, & Adriani, 2018). Flavonoid compounds that can be used as antihyperlipidemia are quercetin (Yi et al., 2021). Damiano et al., (2019) reported that quercetin acts directly on lipid metabolism by inhibiting the transcription of ACC and HMGCR, two regulatory enzymes involved in palmitate and cholesterol biosynthesis.

How quercetin works as an antihyperlipidemic is by inhibiting intestinal cholesterol absorption by reducing the expression of the Niemann-Pick C1-like 1 (NPC1L1) epithelial cholesterol transporter (Nekohashi et al., 2014). Quercetin can also reduce de novo triglyceride lipogenesis, resulting in decreased VLDL-TAG formation (Damiano et al., 2019). Several studies have shown that tamarind (*Tamarindus indica*) is suitable for consumption as an alternative medicine or for body care. Wiyono et al., (2022) stated that ethanol extract of tamarind leaves can significantly inhibit pancreatic lipase as an anti-obesity agent. Research by Assagaf, Bodhi, & Yamlean, (2015) showed that ethanol extract of tamarind leaves can reduce blood cholesterol levels in male white rats induced by high-fat feed. The study aims to examine the effect of ethanol extract of tamarind leaves on lipid profile levels in hyperlipidemic rats.

MATERIALS AND METHODS

This study is an experimental laboratory study with a Posttest Only Control Group Design. Extraction of tamarind leaves was carried out at the Biochemistry Laboratory, maintenance, treatment, and serum making in the experimental cage of Biology Study Program, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang. Measurement of lipid profiles, namely total cholesterol, HDL, LDL and triglyceride levels, was carried out at Balai Laboratorium Kesehatan dan Pengujian Alat Kesehatan Provinsi Jawa Tengah. The research was conducted for 6 months.

1. Research subject

Healthy white rats (*Rattus norvegicus* L.) Wistar strain, 2-3 months old with male sex and weighing about 200 grams.

2. Method and research design

a. Tamarind Leaves Extraction

Tamarindus indica leaves extraction using the maceration method, tamarind leaves are cleaned and then dried using an oven at a temperature of 60°C (Leng, Nadzrin, Shaari, Norawanis, & Khor, 2017). Fully expanded mature leaves of *Tamarindus indica* were used to ensure consistent flavonoid content, as young leaves show lower compound content (Husain et al., 2020). 500 grams of dried tamarind leaves are blended into a coarse powder and sieved. The powder is then mixed with 96% ethanol solvent in a 1L beaker and homogenized with a glass stirrer. The mixture is stored for 3-5 days (Nuralifah, Wahyuni, Parawansah, & Dwi, 2020). The filtrate is filtered with filter paper and collected in an Erlenmeyer flask, then put into the oven to become a dry extract. The ethanol extract of tamarind leaves obtained is then stored in a storage bottle.

b. Phytochemical Analysis

The total flavonoid content of the *Tamarindus indica* leaf ethanol extract was determined using the aluminum chloride ($AlCl_3$) colorimetric method with quercetin as the reference standard. The assay was conducted at the Chem-Mix Pratama Laboratory, Bantul, Yogyakarta (Certificate No. 030/CMP/07/2023).

A 5 g sample of the dried extract was weighed into a 100 mL Erlenmeyer flask, and 96% ethanol was added to volume using a volumetric flask. The mixture was filtered through filter paper, and 1 mL of the clear filtrate was transferred into a test tube. Subsequently, 2 mL of 5% $AlCl_3$ solution and 7 mL of 96% ethanol were added. The solution was vortexed until homogeneous and allowed to stand for color development. Absorbance was measured at a wavelength of 415 nm using a UV–Vis spectrophotometer against a reagent blank. The flavonoid content was calculated from the quercetin calibration curve prepared from standard quercetin solutions and expressed as % quercetin equivalent (QE) or mg QE per gram of extract.

The total flavonoid content, determined from the quercetin calibration curve, was 0.46% quercetin equivalent (QE).

c. Determination of Extract Dosage

The administration and dosage selection of *Tamarindus indica* leaf ethanol extract at 350, 500, and 650 mg/kg body weight were modified from the study of Kuddus et al. (2020), who reported that a 400 mg/kg BW dose of *T. indica* leaf extract significantly reduced total cholesterol, triglycerides, LDL, and VLDL levels, although no significant increase was observed in HDL. Similarly, Bhadoriya et al. (2012) demonstrated that *T. indica* leaf extract at doses of 500, 700, and 1000 mg/kg BW exhibited a dose-dependent anti-inflammatory effect, with the 1000 mg/kg BW dose showing the most pronounced activity. Furthermore, toxicity studies conducted by Amado et al. (2017) and Garba et al. (2023) indicated that oral administration of *T. indica* leaf extract up to 5000 mg/kg BW caused no observable toxic effects, with the acute toxicity (LD_{50}) estimated to exceed 5000 mg/kg BW.

Based on these references, the selected doses (350, 500, and 650 mg/kg BW) were considered safe and within the effective range to evaluate the lipid-lowering potential of *Tamarindus indica* leaf ethanol extract in hyperlipidemic rats.

d. Treatment of Experimental Animals

Sixteen white rats were grouped into 4 groups with 4 replications. The rats were acclimated for 1 week and each group was kept in a 50 x 30 cm cage at a temperature of 25°C, a 12:12 hour

dark-light cycle. During maintenance, the rats were given standard pellet feed branded as RATBIO and ad libitum drinking water. All experimental protocols were approved by the Health Research Ethics Committee (KEPK) of Universitas Negeri Semarang (Approval No. 232/KEPK/EC/2023). The rats were weighed before being treated to determine their initial body weight. The treatment was given lard 3 ml/head for 2 weeks (Ramadi et al 2018; Sahara, 2015), then cholesterol and triglyceride levels were measured to determine whether the rats had experienced hyperlipidemia. Two-week induction ensures stable hyperlipidemic state based on prior reports that 14 days of high-fat diet significantly elevates serum triglycerides and total cholesterol (Aprilia et al., 2017). The rats had already developed hiperlipidemia prior to the administration of treatment of tamarind leaf ethanol extract. This was demonstrated by the cholesterol and triglyceride levels exceeding the normal range after two weeks of lard treatment. The normal total cholesterol level in rats is 10 - 54 mg/dL, and triglycerides range from 26 - 145 mg/dL (Mahdi et al., 2020).

The control group was the group given lard 3 ml/head/day. The treatment of tamarind leaves ethanol extract was divided into 3 doses, namely dose P1 350 mg/kg BW, P2 500 mg/kg BW, and P3 650 mg/kg BW (Modified from Bhadoriya et al., 2012; Kuddus et al., 2020). On 15th day, rats were given extract of *Tamarindus indica* leaves and 2 hours interval was given lard for 2 weeks. The treatment phase (weeks 3–4) was chosen to evaluate the therapeutic rather than prevention effect, consistent with post-induction therapeutic design (Aprilia et al., 2017; Vania et al., 2019). On the final day of the study, blood was taken from the rats orbital vein to measure total cholesterol, triglyceride, HDL and LDL levels.

e. Variable Measurement

The rats were fasted for 12 hours prior to blood sample (Pramesti & Widyastuti, 2014). The rats were anaesthetised with a combination of ketamine and xylazine. Ketamine and xylazine were administered intraperitoneal at doses of 50 mg/kg BW for ketamine and 5 mg/kg BW for xylazine (Massey et al., 2017; Syafikriatillah et al., 2016). Rat blood was taken from the suborbital vein with microhematocrit and collected in a 3 ml microtube. Anesthesia was induced with The blood was centrifuged at 3500 rpm for 10 minutes to obtain serum as a measurement of lipid levels (Danawati, 2022). Measurements of HDL, LDL, total cholesterol was performed using standard enzymatic kits CHOD-PAP (Cholesterol Oxidase Para Aminophenazone), and GPO-PAP (Gliserol Phosposphate Oxidase Para Amino Phenazone) for triglycerides based on the principle of enzymatic spectrophotometry (Nofianti et al., 2019). All analyses were performed using Thermo Scientific brand reagents at the Balai Laboratorium Kesehatan dan Pengujian Alat Kesehatan Provinsi Jawa Tengah.

3. Data Analysis

Data in the form of total cholesterol, triglyceride, HDL and LDL levels obtained were expressed as Mean ± Standard Deviation. Statistical tests using ANOVA with $p < 0.05$ and continued with Least Significance Different (LSD) at a 95% confidence level (Sinulingga, 2023).

RESULT AND DISCUSSION

Hyperlipidemia is a condition of increased lipid levels in the blood (Heryadi & Iskandar, 2020). This study used rats that were given a lard diet to increase lipid levels so that the rats experienced hyperlipidemia. Normal total cholesterol levels in rats are 10 - 54 mg / dL and triglycerides 26 - 145 mg / dL (Mahdi, Citrawati, & Hendrawan, 2020). Normal HDL cholesterol

levels in rat are between 35 - 85 mg / dL (Prabaningrum, Hiyas, Bintanah, & Hapsari, 2022). LDL levels in the blood of rats are considered normal between 7-27 mg / dL (Rusmini, Putri, Hidayat, & Risandy, 2020). The data from the statistical analysis are presented in Tables 1 and Figure 1, as follows:

Table 1. Mean ± SD ANOVA of Lipid Profile Measurement in Hyperlipidemic Rats after Two Weeks of *Tamarindus indica* Leaf Ethanol Extract Administration Concurrent with Lard Feeding Following Two Weeks of Hyperlipidemia Induction.

Group	Cholesterol	Triglycerides	HDL	LDL
K	77.6 ± 13.13^{b}	166.1 ± 50.86^{b}	40.5 ± 6.85^{b}	13.92 ± 10.7
P1	59.5 ± 5.77^{a}	68.50 ± 16.7^{a}	34.25 ± 3.86^{ab}	11.55 ± 9.34
P2	58.5 ± 8.84^{a}	97.12 ± 11^{a}	28 ± 7.52^{a}	11 ± 1.59
P3	53.2 ± 9.52^{a}	70.57 ± 26.23^{a}	27.5 ± 5^{a}	11.58 ± 4.12
ANOVA	0,020	0,002	0,031	0,947

Note: numbers accompanied by different letters ($^{a, b}$) indicate significant differences at $\alpha = 0.05$ based on LSD test.

The Anova test aims to determine whether there is an effect of tamarind leaf ethanol extract. Based on Table 1. the results show that the administration of tamarind leaf ethanol extract has an effect on reducing cholesterol, triglyceride and HDL levels, but has no effect on LDL levels. The next analysis used the Post Hoc LSD test at a significance level of 95% to determine the real differences between groups, in total cholesterol and triglyceride levels showed that the control group had a real difference with all treatment groups, but there was no real difference between treatment doses. The HDL levels of the control group showed a real difference with groups P2 and P3, and were not significantly different from group P1.

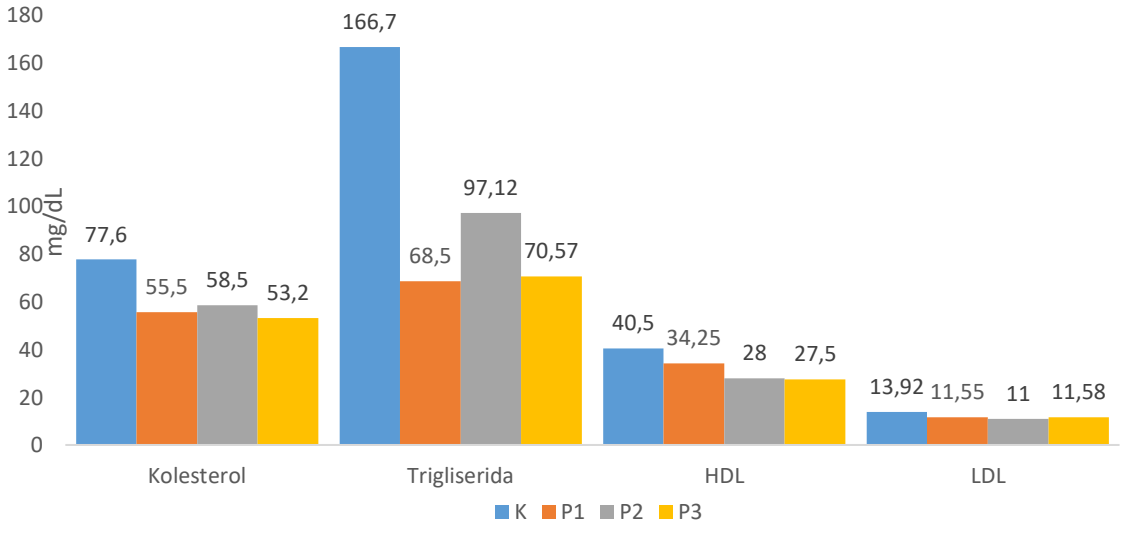

Figure 1. Comparison of Mean Lipid Profile Levels Between Groups

Figure 1 shows that the group treated with tamarind leaf ethanol extract experienced a decrease in lipid profile levels within the normal range except for total cholesterol levels. Total cholesterol still experienced a lower decrease than the control group.

Based on the statistical results of the tamarind leaf ethanol extract treatment, it had an effect on reducing total cholesterol and triglyceride levels. The results of this study are in line with previous research conducted by Aprilia, Ninditasari, & Walujo, (2017) tamarind leaf extract significantly reduced lipid profile levels but LDL levels did not show significant differences.

In this study, HDL levels decreased along with reductions in total cholesterol and triglycerides. HDL participates in reverse cholesterol transport; thus, when overall cholesterol synthesis and circulation are reduced, there is less cholesterol available for efflux into HDL particles, leading to proportional decreases in HDL-C (Hu et al., 2021:Huff et al., 2024).

The results of this study, providing high-fat feed from lard showed an increase in total cholesterol and triglyceride levels exceeding normal limits so that rats could be said to be experiencing hyperlipidemia. Lard contains 38-43% saturated fatty acids and cholesterol (Mahdi et al., 2020). In 100 grams of lard there is a cholesterol content of 97 mg (Restuati, Rahmat, & Nanda, 2017). This is also supported by the results of a study by Aprilia et al., (2017) which stated that giving high-fat feed for 2 weeks can significantly increase total cholesterol and triglyceride levels.

LDL cholesterol levels showed that tamarind leaf ethanol extract had no effect on LDL levels. This is possible because first, the diet contains too much cholesterol and fat, so the body is unable to control it. Second, cholesterol excretion through bile acids is too little. Third, cholesterol production in the liver is too much (Restuati et al., 2017). A high-fat diet results in higher VLDL secretion. Increased VLDL production causes hyperlipidemia (Casso & Farzam, 2022). High blood triglyceride levels are caused by high VLDL levels (Loaloka & Pantaleon, 2020).

Consumption of dietary fat will be broken down by bile acids and absorbed by the intestinal lumen. In intestinal cells, free fatty acids (FFA) combine with glycerol molecules to form triglycerides and cholesterol is converted into cholesterol esters by the enzyme acyl coenzyme A (CoA). Cholesterol esters and triglycerides then combine with apolipoprotein B-48 to form chylomicrons (Stewart, McCallin, Martinez, Chacko, & Yusuf, 2020). The size and composition of chylomicrons formed in the intestine depends on the amount of fat digested and absorbed by the intestine. High-fat foods produce larger chylomicrons causing the formation of large chylomicron particles due to the increased amount of triglycerides transported (Feingold, 2024). During digestion, the gallbladder pumps bile into the small intestine to help metabolize cholesterol because cholesterol and triglycerides are easily transported into micelles. Micelles facilitate absorption by transporting dissolved lipids to the plasma membrane of enterocytes, which form a single cell layer in the lumen of the small intestine, which then facilitates transport via Nieman-Pick C1 Like 1 (NPC1L1) (Sucharski & Koenig, 2022). Some of the cholesterol taken up is then pumped back into the lumen via the ABCG5 and ABCG8 heterodimers. Some of the absorbed cholesterol is converted to cholesterol esters by the enzyme acyl-CoA:cholesterol acyltransferase (ACAT) (Xiao et al., 2023).

The remaining fraction is absorbed as free cholesterol. In enterocytes, triglycerides, cholesterol and cholesterol esters are combined with apolipoprotein B48 into chylomicrons (Jim, 2014). Chylomicrons are then released into the lymph through the basolateral membrane of enterocytes and carried into the bloodstream via the lymphatic system. In the blood circulation, the enzyme lipoprotein lipase breaks down triglycerides in the chylomicron core for use by peripheral tissues such as fat and muscle, while most of the cholesterol in the remaining chylomicrons is sent back to the liver (Jia, Betters, & Yu, 2014). Unhydrolyzed chylomicrons enter the liver and form VLDL and are converted into IDL (Intermediate-density lipoprotein) which is then converted into LDL

(Nalla et al., 2023). Triglycerides and cholesterol esters are synthesized endogenously in the liver to form VLDL (Stewart et al., 2020). Very low density lipoprotein (VLDL) together with chylomicrons originating from the intestine are processed in the capillaries of adipose tissue, heart, and skeletal muscle by the enzyme LPL. Lipoprotein lipase (LPL) is the rate-limiting enzyme for the hydrolysis of the triglyceride core of circulating TG-rich lipoproteins, chylomicrons, and VLDL (Ji et al., 2019).

Lipoprotein lipase (LPL) hydrolyzes triglycerides to produce free fatty acids which are taken up by the cells of the respective organs for storage or energy generation (Heeren & Scheja, 2021). Some VLDL with higher triglyceride content than cholesterol will be hydrolyzed by lipoprotein lipase to IDL. Liver lipase will re-hydrolyze IDL to form LDL (Syahla et al., 2023). This low-density lipoprotein (LDL) binds to the LDL receptor and is converted into cholesterol in the form of HDL (High-Density Lipoproteins) and is forwarded to the endocrine glands for steroid hormone synthesis (Nalla et al., 2023).

Excess free cholesterol in nascent HDL is converted into cholesterol ester with the help of the enzymes Lecithin Cholesterol Acyltransferase (LCAT) and Cholesteryl Ester Transfer Protein (CETP) to be transferred back to the liver (Erizon & Karani, 2020). HDL cholesterol can also be secreted directly into the bile (Jia et al., 2014). The presence of cholesterol in the liver will be identified by the regulatory protein SREBP 2 (Caponio, Wang, Di, De, & Portincasa, 2021). Furthermore, SREBP 2 will induce the activation of important enzymes in cholesterol synthesis, namely HMGCR (HMG-CoA Reductase) and HMG coA synthetase (Eilam, Pintel, Khattib, Shagug, Taha, & Avni, 2022). HMG-CoA is synthesized by acetyl CoA with the help of HMGCS (3-hydroxy-3-methylglutaryl coenzyme A synthase) (Hu et al., 2021). HMGCR will catalyze the reduction of HMG-CoA to mevalonate, then converted to squalene and lanosterol, which finally becomes cholesterol (Xiao et al., 2023). Triglycerides are a form of fat that plays a role as one of the body's main energy stores (Islahi & Mulyati, 2023). Adipose tissue absorbs energy in the form of triglycerides, which come from two main sources of lipids: exogenous circulating fatty acids and endogenously synthesized fatty acids from de novo lipogenesis (Rowland et al., 2023).

De novo lipogenesis is the process of fatty acid formation which is synthesized from acetyl-CoA, then esterified with 3-phosphoglycerol to produce triglycerides (TG). Acetyl-CoA carboxylase (ACC) is the rate-limiting enzyme of fatty acid synthesis, which carboxylates acetyl-CoA to produce malonyl-CoA (Lu et al., 2021). Triglycerides then form lipid droplets in the liver or are secreted as very low-density lipoproteins (VLDL). Under normal conditions, the liver stores a small amount of triglycerides in the form of lipid droplets, and a large amount of triglycerides is circulated in the form of VLDL lipoprotein particles that deliver fatty acids to muscle and adipose (Alves & Cohen, 2018).

The mechanism of action of flavonoids in lowering cholesterol levels is through inhibition of the HMG CoA reductase (HMGCR) enzyme so that the cholesterol synthesis process decreases (Widiastuti, Slamet, & Kanetro, 2022). When the function of HMGCR to convert mevalonate from HMG-CoA is inhibited, the formation of mevalonate is disrupted, causing a decrease in mevalonate concentration and causing a decrease in cholesterol production in the liver (Pangestika et al., 2020).

Decreased cholesterol production in the liver results in reduced VLDL formation. This results in increased activity of LCAT, an enzyme released by the liver and responsible for binding lipoproteins or free fats in plasma. Active flavonoids increase LCAT activity, stimulating the formation of HDL by converting free cholesterol into cholesterol esters in the lipoprotein core

(Widiastuti et al., 2022). Flavonoids increase the number of HDL receptors in the liver so that total cholesterol levels will decrease and stabilize the function of HDL, namely transporting excess LDL in various adipose tissues (Naru et al., 2023).

Flavonoids work on the lipoprotein lipase enzyme in the formation of cholesterol or triglycerides. The role of flavonoids increases the activity of the lipoprotein lipase enzyme which will increase the hydrolysis of triglycerides into fatty acids and glycerol to be released into the blood vessels. Cells that require fatty acids and glycerol will burn these components and produce energy, namely carbon dioxide (CO2) and water (H2O). If the activity of the lipoprotein lipase enzyme increases, the process of triglyceride formation through the exogenous pathway mechanism in the blood vessels is inhibited so that triglyceride levels can decrease (Veronica et al., 2018). One of the flavonoid compounds contained in tamarind leaves is quercetin (Yunita, Fatimah, Yulianto, Trikuncahyo, & Khodijah, 2019). Quercetin can be used as an antihyperlipidemia (Yi et al., 2021). The mechanism of quercetin in reducing triglyceride levels is, first quercetin can reduce the synthesis of de novo fatty acids and triacylglycerols (TAG), which results in decreased formation of VLDL-TAG (Damiano et al., 2019). Quercetin suppresses de novo lipogenesis (new fatty acid synthesis) by reducing the rate of fatty acid incorporation into adipocyte triacylglycerol in rat fat pads and by inhibiting the expression levels of two enzymes of this pathway, Fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) activity (Zhao et al., 2017).

Phytochemical quantification of *Tamarindus indica* leaf ethanol extract revealed a total flavonoid content of 0.46% quercetin equivalent (QE). Considering the administered doses of 350, 500, and 650 mg/kg body weight, the treated rats received an estimated 1.6–3.0 mg quercetin equivalents/kg BW/day. This quantitative range substantiates the biological plausibility of the lipid-lowering effects observed in the experimental model. Quercetin can reduce high blood cholesterol levels by specifically inhibiting intestinal cholesterol absorption through reducing the expression of the epithelial cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1) (Nekohashi et al., 2014). Inhibition of NPC1L1 results in the accumulation of cholesterol in the small intestinal brush border membrane or microvillus plasma membrane (BBM) temporarily, and this accumulation increases the interaction of sterols with ABCG5/G8 to promote the rapid efflux of BBM cholesterol into the lumen. This inhibition will ultimately direct excess cholesterol in BBM to be excreted back into the lumen (Nakano et al., 2016). Inhibition of intestinal cholesterol absorption will cause cholesterol excretion through feces (Nekohashi et al., 2014).

NPC1L1 inhibitors can be said to be complementary to HMGCR inhibition to reduce serum cholesterol (Zhang et al., 2022). Liu et al., (2018) found that quercetin administration for 24 weeks (100 mg/kg) could significantly reduce liver cholesterol and ox-LDL levels by enhancing the autophagy lysosome signaling pathway and inhibiting the expression of Scavenger receptors, including macrophage scavenger receptor 1 (MSR1) and CD36. Other studies have shown that quercetin increases the expression of Scavenger receptor class B type 1 (SR-B1), as a multifunctional receptor for cholesterol influx and efflux. It also activates the Peroxisome proliferator-activated receptor pathway (PPARγ and LXRα) and lipid accumulation in the liver (Ren, Jiang, & Zhao, 2018).

Ji et al., (2019) study stated that inhibition of NPC1L1 substantially decreased intestinal cholesterol absorption, which was modulated by sterol regulatory element binding protein-2 (SREBP)-2 and liver X receptor (LXR). Liver X receptor (LXR) acts as a cholesterol sensor, working in a similar manner to sterol response element-binding proteins (SREBPs), lowering cholesterol

levels by increasing RNA expression of target genes related to reverse cholesterol transport, bile acid synthesis, and intestinal cholesterol absorption (Laka, Makgoo, & Mbita, 2022).

CONCLUSION

Ethanol extract of tamarind leaves has an effect on reducing total cholesterol and triglyceride levels but does not significantly increase HDL levels and decrease LDL levels in hyperlipidemic rats.

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