Original Research

DECREASE OF LDL CHOLESTEROL THROUGH THE INCREASE OF HDL CHOLESTEROL BY ADMINISTERING *Garcinia mangostana L.* PEEL EXTRACT IN WHITE MICE

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ABSTRACT

Atherosclerosis contributes to coronary heart disease which may lead to fatality. High cholesterol consumption, stress, and smoking can increase LDL cholesterol in the blood. Consumption of unsaturated fats, high fiber foods, exercise, quitting smoking, losing weight, and giving hypolipidemic drugs, especially herbs, can increase HDL cholesterol and decrease LDL cholesterol. Garcinia mangostana L. peel extract can decrease LDL cholesterol by increasing reverse HDL cholesterol transport to the liver. The study used post test control group design. This study was experimental laboratory research with population of hypercholesterolemic male white mice aged 3-4 weeks with 100-200 grams weight. The HDL and LDL cholesterol data were collected through an enzymatic method by spectrophotometer. This study used analysis of variance (Anova) with significance level of α <0.05. The experiment divided the subjects into positive and negative control groups with dosage variations of 50, 150, 250, and 350 mg/kgBW. Examination of hypercholesterolemia in white mice was conducted on the 8th day. The examination of HDL and LDL cholesterol given peel extract of Garcinia mangostana L. was conducted on the 22nd day. The analysis showed that giving Garcinia mangostana L. peel extract for various dosages could significantly decrease LDL cholesterol and increase HDL cholesterol (p <0.05). Peel extract of Garcinia mangostana L. that contained mangosteen could increase non-radical products that could prevent the transfer of ester cholesterol from HDL to VLDL which impact in increasing HDL cholesterol and decreasing LDL cholesterol.

***Keywords**: Garcinia mangostana L; peel extract; LDL cholesterol; HDL cholesterol; hypercholesterolemia; health risk*

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Highlights:

1. Ethanol extract of *Garcinia mangostana* L. peel reduce malondialdehyde.
2. *Garcinia mangostana* L. peel extract can increase non-radical products which impact in decreasing LDL cholesterol and increasing HDL cholesterol.

INTRODUCTION

Hypercholesterolemia has a role in the etiology of atherosclerosis. Atherosclerosis contributes to coronary heart disease as the main cause of mortality. WHO data in 2012 stated that 31% of mortality was due to heart disease and 38.8% was due to coronary heart disease that will increase to more than 20 million in 2030. In 2013, the data displayed that 1.5% of diseases in Indonesia were coronary heart disease with hypertension, hypercholesterolemia, and diabetes mellitus as the main risk factors (Ghani et al. 2016, Hussain et al. 2016).

Atherosclerosis occurs due to saturation of LDL receptors. The saturation of LDL receptors converts to oxidized LD*, which is partially absorbed by scavenger receptors and partially taken up by macrophages. If LDL is excessively oxidized, macrophages will transform into foam cells found in early atherosclerotic lesions (Stephen et al. 2012). High consumption of cholesterol, stress, and smoking can increase the secretion of VLDL by the liver which impacts in increasing IDL that forms LDL (Trajkovska & Topuzovska 2017, Macho-González et al. 2019, Sinulingga et al. 2019), and increasing cholesterol in cells (Maisaroh et al. 2020).

Consuming unsaturated fats can lower blood cholesterol by inhibiting the conversion of cholesterol to be bile acids (Liu et al. 2017). Exercise, stop smoking, reducing body weight, and providing hypolipidemic drugs, especially herbs can increase HDL cholesterol, decrease LDL cholesterol, and increase the expression of lipoprotein lipases. *Garcinia mangostana L.* peel extract can increase HDL (Raharjo & Monica 2015), and decrease LDL through transporting back to the liver (Arozal et al. 2020).

If diet modification and lifestyle management fails, hypolipidemic drugs can be alternative to be given. Hypolipidemic drugs have the effect of gastrointestinal disorders, skin rashes, and even liver dysfunction. Besides, there are contraindications which make not all people can consume the drug due to a high potential-risk (Wirasuta et al. 2014). Herbal hypolipidemic treatment is active to be conducted, because ethanol extract of *Garcinia mangostana L.* Peel that contains antioxidant mangosteen can increase HDL and decrease LDL through transporting back to the liver by increasing non-radical products (Arozal et al. 2020).

MATERIALS AND METHODS

The design of this study was a post test control group between *Garcinia mangostana L.* peel extract and HDL and LDL. This study was experimental laboratory research with a population of hypercholeterolemic male mice aged 3-4 weeks with 100-200 grams. This study used an enzymatic method by spectrophotometer to collect HDL and LDL cholesterol data, and analyzed using analysis of variance (Anova) with significance level of $\alpha < 0.05$.

Hypercholesterolemia in white mice was made by feeding a high-fat diet. Experiment of giving ethanol extract of *Garcinia mangostana L.* peel was suspended in 1% carboxymethyl cellulose in hypercholesterolemic white mice which was grouped into 7 groups with 6 mice in each group. Negative control group, positive control group, and treatment group were in accordance with the dosage variations of 50, 150, 250, and 350 mg/kgBW. The examination of hypercholesterolemia of white mice was conducted on the 8th day. Meanwhile, the examination of HDL and LDL cholesterol given ethanol extract of *Garcinia mangostana L.* peel was conducted on the 22nd day.

RESULTS

The results showed that LDL cholesterol after being induced by MDTL increased significantly with a significance level of p=0.021 rather than before being induced. Meanwhile, HDL cholesterol after being induced did not increase significantly with a significance level of p=0.620.

Table 1. Different HDL and LDL cholesterol tests in experiment group before and after being induced by high fat diet foods (*makanan diet tinggi lemak (MDTL))*

Dependent variable	Group		Sig. (p)
	Before (Group 1) N = 6	After (Group 2) N = 6	
HDL cholesterol (Mean ±SD)	21.67 (± 2.21)	20.00 (± 6.19)	0.620
LDL cholesterol (Mean ±SD)	7.50 (± 0.83)	14.67(± 2.06)	0.021

Table 2. Different test with ANOVA variable based on control and treatment group of *Garcinia mangostana L.* peel extract

Dependent variable	F count	Sig.
HDL cholesterol	3.410	0.023
LDL cholesterol	5.482	0.003

The results showed that there was a significant difference of reduction in LDL cholesterol between control group and treatment group by giving ethanol extract of *Garcinia mangostana L.* peel in accordance with dosage variations of 50mg, 150mg, 250mg, and 350 mg/kgBW with significance level of p=0.003 and significant increase in HDL cholesterol with significance level of p=0.023 (<0.05).

Table 3. Least significant differences (LSD) test against HDL cholesterol variable

Group	Control	Dose 50 mg	Dose 150 mg	Dose 250 mg
Dose 50 mg (Sig.)	0.311	-	-	-
Dose 150 mg (Sig.)	0.560	0.662	-	-
Dose 250 mg (Sig.)	0.249	0.036	0.089	-
Dose 350 mg (Sig.)	0.042	0.004	0.011	0.346
Standard of Error	= 2.257			

The results showed that there was a significant increase between control group and group of 350 mg dose (p=0.036) and between group of 50 mg dose, group of 250 mg dose (p=0.036), and group of 350 mg dose (p=0.004). However, there was a significant increase between group of 150 mg dose and group of 350 mg dose (p=0.011)

The results showed that there was a significant decrease between groups with 50 mg dose (p=0.003), 150 mg dose (p=0.036), 250 mg dose (p=0.001), and 350 mg dose (p=0.002).

Table 4. Least significant differences (LSD) test against LDL cholesterol variable

Group	Control	Dose 50 mg	Dose 150 mg	Dose 250 mg
Dose 50 mg (Sig.)	0.003	-	-	-
Dose 150 mg (Sig.)	0.000	0.427	-	-
Dose 250 mg (Sig.)	0.001	0.569	0.819	-
Dose 350 mg (Sig.)	0.002	0.819	0.569	0.732
Standard of Error	= 1.444			

DISCUSSION

Induction of high-fat diet foods (MDTL) to make hypercholeterolemic mice

The results of the study showed that after MDTL induction, LDL cholesterol increased significantly with p=0.021, while HDL cholesterol did not increase with p=0.620. MDTL was made from palm oil which contained triacylglycerol saturated fat and beef fat that contained sterols, and it was induced into mice. Before being absorbed by the intestine, triglycerides were firstly emulated by bile acids (Sagar et al. 2016). In epithelial cells of intestine, triacylglycerols together with proteins, phospholipids, and cholesterol esters, combine to form chylomicrons.Chylomicrons are hydrolyzed into fatty acids and glycerol which then enters tissue cells to be converted into energy. Sterols are the components of cholesterol.

Mechanism in increasing cholesterol due to induction of high-fat diet foods (MDTL) is estimated to cause an increase in saturated fatty acids in the blood. It can impact in reducing LDL receptors and increasing to form VLDL particles which are smaller precursors of LDL and smaller VLDL that contains a lot of cholesterol (Carson et al. 2019).Furthermore, a decrease in LDL receptors and an increase in VLDL particles impacts in amassing of LDL cholesterol in the blood (hypercholesterolemia).

The increase of VLDL particles impacts the transfer of triacylglycerols from VLDL to HDL and cholesterol esters from HDL to VLDL mediated by CETP (cholesteryl ester transfer protein). This transfer impacts the formation of HDL core that is richer in triacylglycerol instead of cholesterol esters (known as small dense HDL). The increase in the formation of small dense HDL impacts in reducing HDL formation (Ahn & Kim 2016).

The increase of HDL cholesterol after given ethanol extract of *Garcinia mangostana L.* peel

The result of the study was also found through different Anova test found in treatment group that was given ethanol extract of *Garcinia mangostana L*. peel in accordance with dosage variation which showed that there was a significant increase for HDL cholesterol with significance level of p=0.023.LSD test was conducted between control group and 350 mg dose (p=0.036), between group of 50 mg dose and group of 250 mg dose (p=0.036) as well as group of 350 mg dose (p=0.004). Furthermore, there was a significant increase between the group of 150 mg dose and the group of 350 mg dose (p= 0.011).

The ethanol extract of *Garcinia mangostana L*. peel which contains mangosteen (Pratiwi et al. 2016), where it can effectively save α-tocopherol (Nakatomi 2004). α-tocopherol is a chain-breaking antioxidant and donor of hydrogen phenolic (Akbari et al. 2016, Viglianisi & Menichetti 2019, Polumbryk et al. 2013), as well as a substitute for tocopheryl radicals which are less reactive (α-TO•). α-tocopherol is also a direct reagent with radical initiation to prevent the formation of LOO in non-radical production, and one of which is Malondialdehyde decreases (damaged).

The decreased or broken Malondialdehyde can reduce adducts with amino acid side chains from apolipoprotein B-100 (Murray et al. 2009), and it impacts on the decrease of interaction and absorption of oxidized LDL. This decrease impacts on the decrease of oxidized LDL taken by macrophages, so that the co-substrate of fatty acyl by enzyme Acyl-CoA cholesterol transferase (ACAT) in macrophages containing oxidized LDL is fulfilled. This adequacy can inhibit the action of HMG-CoA reductase enzyme in cell membrane (Brown et al. 2001, Snaebjornsson et al. 2020). Hence, VLDL blood decreases (Murray et al. 2009).

The decrease of VLDL will prevent the transfer of triacylglycerol from VLDL to HDL and cholesterol ester from HDL to VLDL mediated by CETP (cholesteryl ester transfer protein) that impacts on forming HDL core which is richer in triacylglycerol instead of cholesterol ester (known as small dense HDL) that decreases. The decrease in forming small dense HDL impacts on the increase of forming HDL (Murray et al. 2009). Providing pure mangosteen suspension showed a significant increase in serum of HDL cholesterol (Raharjo & Monica 2015 stephen).

Decrease of LDL cholesterol after given ethanol extract of *Garcinia mangostana L.*peel

The result of the different Anova test was found in the treatment group given ethanol extract of *Garcinia mangostana L*. peel in accordance with dosage variations which showed that there was a highly

significant decrease in LDL cholesterol with significance level of p=0.003. Meanwhile, the LSD test showed a significant decrease between control group and groups of 50 mg dose (p=0.003), 150 mg dose (p=0.036), 250 mg dose (p=0.001), and 350 mg dose (p=0.002).

The ethanol extract of *Garcinia mangostana L.* peel that contains antioxidant mangosteen can increase HDL. HDL plays a role in Reverse Cholesterol Transport. HDL absorbs cholesterol from the tissues and lecithin cholesterol acyltransferase (LCAT) esterified and precipitates it in the middle of the particles. Cholesteryl ester in HDL is absorbed in the liver either directly or after moving to VLDL, IDL or LDL through the cholesteryl ester transfer protein. Excess cholesterol is excreted from the liver into the bile as cholesterol or bile salts (Murray et al. 2009). The increase in HDL impacts the increase in Reverse Cholesterol Transport through the liver to the bile which impacts the decrease of LDL cholesterol (Murray et al. 2009).

The decrease of LDL also occurs due to the inhibition of malondialdehyde (MDA) formation by extract of *Garcinia mangostana L.* peel (Williams et al. 1995). Decrease or broken malondialdehyde impacts in reducing the adduct between malondialdehyde and amino acid side chain from apolipoprotein B-100 (Murray et al. 2009), and reducing the interaction and absorption of oxidized LDL by lower affinity systems (known as scavenger receptors) (Murray et al. 2009). Due to the reduced interaction and absorption of oxidized LDL, oxidized LDL is also less which is taken by the macrophages. Thus, co-substrate of fatty acyl by Acyl-CoA enzyme; cholesterol transferase (ACAT) in macrophages that is contained oxidized LDL is fulfilled and it will be able to inhibit the enzyme HMG-CoA reductase in cell membrane (Murray et al. 2009) as well as impacting on the decrease of LDL cholesterol synthesis (Murray et al. 2009).

Strength and limitation

The study employed different dosages of the extract, which helps in identifying the optimal dose and dose-response relationship. This study used an experimental design with a post-test control group, which is a rigorous approach to test the efficacy of the intervention.The study did not investigate the long-term effects of Garcinia mangostana L. peel extract on cholesterol levels and cardiovascular outcomes,and control for other potential confounding factors, such as diet and physical activity, which could influence the results, and examine the mechanism by which the peel extract reduces LDL and increases HDL cholesterol levels.

CONCLUSION

Ethanol extract of *Garcinia mangostana L.* peel that contains mangosteen can increase Non-Radical Products (NRP) and reduce or damage radical products, such as malondialdehyde. Decreased or broken malondialdehyde can prevent the transfer of triacylglycerol from VLDL to HDL and ester cholesterol from HDL to VLDL which impacts the increase of HDL cholesterol. Besides, the decreased or broken malondialdehyde can reduce the interaction and absorption of oxidized LDL by the scavenger receptor as well as the increase of reverse cholesterol transport through the liver to bile by HDL that impacts to reduce LDL cholesterol.

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Conflict of interest

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Author contribution

The author was contributed to the all conceptualization, study design and methodology. data collection, write, and final revision.

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