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Effects of Kersen Juice and Lakum Leaf Extract on Lipid Profile of White Rats With Hyperlipidemia

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Cayratia trifolia; Hyperlipidemia Rat; Lipid Profile; *Mutingia calabura*

Abstract

Kersen fruit and Lakum leaf contain substances that are potential as an antihyperlipidemic. The aim of this research was to analyze the effects of Kersen juice (*Mutingia calabura* L.) with dosage 0.2 ml/200 g BW and lakum leaf extract (*Cayratia trifolia* L.) with dosage of 40 mg/200 g BW on lipid profile of white rats (*Rattus norvegicus* L.) with hyperlipidemia. This study used a Complete Randomized Design (CRD). This study used twenty adult male Wistar rats which were divided into five groups : P0 as a control group, P1 as a High Feed Diet (HFD) control group, P2 as a HFD group treated with Kersen juice with dosage of 0.2 ml/200 g BW, P3 as a HFD group treated with Lakum leaf extract with dosage of 40 mg/200 g BW and P4 as a HFD group treated with simvastatin. The treatments were given orally for 28 days. The parameters of this study were the level of cholesterol, HDL, LDL and triglyceride, as well as body weight, and food consumption. One-way ANOVA test was performed to determine the significant differences $p<0.05$ between groups followed by Duncan test with a 95% significant level. The results showed that compared to Kersen juice with dosage of 0.2 ml/200 g BW, administration of Lakum leaf extract with dosage of 40 mg/200 g BW was more effective in lowering cholesterol level, triglyceride and increasing HDL level, however, they were not effective in lowering LDL in rats with hyperlipidemia. This result shows that kersen and lakum leaf could be an alternative to prevent and avoid further effects of high cholesterol in people with hyperlipidemia.

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INTRODUCTION

The excess of blood lipids which include cholesterol, triglyceride, Low Density Lipoprotein (LDL) and a decrease in High Density Lipoprotein (HDL) in the bloodstream are the characteristics of hyperlipidemia (Onwe et al., 2015). It has been reported that the main risk factor for cardiovascular disease is the increase of serum total cholesterol LDL (Nirosha *et al*., 2014). The main cause for hyperlipidemia is a disruption in lipid metabolism which is caused by the defect in lipoprotein lipase activity or the absence of the surface Apolipoprotein C-II (Harikumar et al., 2013). Based on the data from WHO in 2015, approximately 17.7 million people died because of cardiovascular disease. In Indonesia, based on data from Kementrian Kesehatan RI (2013), coronary heart disease has the highest prevalence among other cardiovascular diseases. They predict that the death rate due to this disease will rise to 23.3 million in 2030.

High lipid diet is regarded as an important factor in the development of Ischemic heart disease. The focus so far has been mainly on the systemic and coronary vascular effects of cholesterol (Gazzerro et al., 2012). Vitamin C, minerals, and some phytochemicals such as phenol and flavonoid are known as antioxidants. They work by blocking the oxidative stress from free radicals and repair the damage to the endothelial tissue. They are also protecting LDL and Very Low Density Lipoprotein (VLDL) especially in the oxidation reaction (Gross, 2004). Repaired endothelial tissue in hyperlipidemia causes a decrease in total LDL, triglycerides, and cholesterol (Kakadiya, 2009).

Kersen (Mutingia calabura) and Lakum (*Cayratia trifolia*) are traditional plants that are less occupied but have high potential to repair the lipid profile of hyperlipidemia (Preethi, 2011). A recent study has reported that Kersen and Lakum contain vitamin C at approximately 80.5 mg (Mahmood et al., 2014). Moreover, they also contain flavonoids, phenols, niacin, and beta–carotene which act as antioxidant agents (Ragasa et al., 2015).

Figure 1. Kersen fruit (*Muntingia calabura* L.) (A) and Lakum leaf (*Cayratia trifolia* (L.) (B)

Batra et al., (2013) in his research said that the used of Lakum root extract with dosage of 200 mg/kg BW and 400 mg/kg BW significantly reduced the level of triglycerides, cholesterol, LDL and increased the level of HDL. However, the research on Lakum leaf has not been reported yet. The research on Kersen fruit that has been conducted by Sudargo et al., (2017), reported that the administration of Kersen fruit juice with a dosage of 0.9 ml/ 200 g BW and 1.8 ml/200 g BW in 14 days can elevate the level of HDL in blood serum, but not significantly reduced the level of triglycerides, cholesterol, and LDL. Therefore, the purpose of this study was to analyze the potentials of Kersen fruit and Lakum leaf extract on repairing the lipid profiles of rats with hyperlipidemia. This study is expected to become one of an alternative solution to prevent and avoid further effects of high cholesterol in people with hyperlipidemia.

METHODS

Standard feed (BR II), High Fat Diet contain of cornstarch 29.67%, casein 14%, fructose 25%, solid oil 21.4%, alpha-cellulose 5%, mineral mix 3.5%, vitamin mix 1%, methionine 0.18% and choline chloride 0.25%, lipid profile kit from Diasys were used during study.

The Preparation of Kersen Juice

Kersen fruit used in this study had the characters as follow: the color was red, clean and no damage found in the structure. The fruits obtained were washed thoroughly and then grinded using a blender without water addition. The Kersen juice obtained was filtered to separate the juice from the pulp using the filter.

The Preparation of Lakum Leaf Extract

The leaves obtained were washed thoroughly and dried in the oven with a temperature of 40 ^{0}C until the water level reached 10%. Dried leaves then were blended using a blender. Five hundred grams of blended leaves were soaked in 1000 cc of ethanol 96% and incubated for three days. The suspension obtained was filtered into the sterile glass and the filtrate was filtrated into the bottle using filter paper Whatman No.1 until the pasta remained. Solution stock of Lakum leaf extract was made by dissolving 1.2 g of pasta into 6 ml aquades.

Animal Study

This study was performed on December-May 2019 in Animal Laboratory of Biology,

Science and Math Faculty, Diponegoro University. During this study, 20 old male Wistar rats aged two months, the weight of 200 g were obtained from Animal Laboratory, Semarang State University. Before treatment, adaptation was performed to the rats for a week by providing a standard diet BR II and drink *ad libitum*. Rats were placed in the cage individually with a controlled temperature room and lighting for 8 weeks. Ethical clearance of this study was obtained from the Ethics Committee of Faculty of Medicine, Diponegoro University. After the adaptation done, the rats were divided into 5 groups consisting of 4 rats each. Group I was fed with a standard diet without any treatment; Group II with by High Feed Diet without any treatment; Group III was fed with HFD and treated by Kersen juice with dosage of 0.2 ml/200 g BW; Group IV was fed with HFD and treated by Lakum leaf extract with dosage of 0.2 ml/200 g BW and Group V was fed High feed Diet and treated with simvastatin 0.18 ml/200 g BW.

The HFD was provisioned for 30 days. The first blood checking was drawn on the 30th day via tail to check whether the rats have already in hyperlipidemia conditions. The treatment was continued by giving Kersen juice and Lakum leaf extract for 28 days. On the 28th day, blood was drawn from the heart for lipid profile analysis. CHOD-PAP method using a diagnostic system kit (DiaSys) was used to analyze the cholesterol, triglycerides, LDL and HDL. Analysis of the lipid profile followed the protocols contained in the kit. The result of the analysis of the lipid profile was expressed as Mean±SD. The differences between treatments were evaluated by One way Anova test and Duncan test that was conducted to determine the significant differences between groups with $p<0,05$. SPSS 16 for windows was used to do the statistic operation. Bodyweight was measured every 3 days, while the leftover of the food was measured daily.

RESULTS AND DISCUSSION

The effects of Kersen juice (*Mutingia calabura* L.) and Lakum leaf extract (*Cayratia trifolia* L.) on lipid profile of white rats (*Rattus norvegicus* L.) with hyperlipidemia are shown on Table 1.

Based on data in Table 1, it is found that the variable of cholesterol between P0 and P1 ($p<0.05$) is significantly different. The increase of cholesterol in the blood is caused by HFD administration. Sudargo et al (2017) said that the normal cholesterol level in white rats is between 47- 88 mg/dL with an average of 65 mg/dL. So that based on the resulting cholesterol with average >65 mg /dL, it is said to be in hyperlipidemia condition. Cholesterol level in the control group (P0) is found to be significantly different from the groups that have been given Kersen juice (P2). The effect of Kersen juice in lowering cholesterol is predicted due to the high content of vitamin C and flavonoids (Sudargo et al., 2017). Flavonoids can decrease cholesterol levels by inhibiting the cholesterol absorption in the intestine and can increase the bile formation reaction for being excreted with the feces (Shattat, 2014). Vitamin C is a water-soluble antioxidant that can prevent oxidation. Vitamin C can decrease the level of cholesterol through activity of hydroxylase 7α-hydroxylation (Fatimah, 2017). The reactions of 7α-hydroxylation increase the conversion process of cholesterol into bile acids in the liver. As the conversion process increased, the amount of cholesterol in the blood decreased (Zhang et al., 2014). Cholesterol level in groups which have been administered by Lakum leaf extract (P3) is not significantly different compared the control group. However, it is significantly different from hyperlipidemia rats without any treatment (P1). Regasa et al (2015) said that Lakum leaf has an antioxidant constituent that can inhibit fat accumulation in the blood. The ability of Lakum leaf to decrease cholesterol level is due to the presence of phenol constituent. Phenol can decrease li-

Table 1. Lipid profile of Wistar male rats after treatment for 28 days

Variables (mg/dL)	Treatment				
	P0	P1	P2	P3	P4
Cholesterol	$62.5^{c} \pm 5.92$	$104.75^{a} \pm 19.57$	$90^{ab} \pm 5.29$	$80^{bc} \pm 12.19$	$68.25^{c} \pm 9.53$
HDL	$27.4^{bc} \pm 4.51$	$23.5^{c} \pm 3.7$	$29.5^{abc} \pm 2.38$	$31.5^{ab} \pm 4.79$	$35^{a} \pm 3.46$
LDL	$27.5^{bc} \pm 4.51$	$35^{a} \pm 3.46$	$29.5^{abc} \pm 2.38$	$31.5^{ab} \pm 4.79$	$23.5^{c} \pm 3.70$
Triglyceride	$64.25^{c} \pm 8.42$	$161.5^{a} \pm 12.26$	$92.75^{b} \pm 9.74$	$88^{b} \pm 8.16$	$64.75^{c} \pm 10.44$

Values are expressed as Mean ± SD, ^{abc}Different notation indicates $p<0.05$ using Duncan test, Normal control group (P0), HFD control group (P1), HFD group treated with Kersen juice 0.2 ml/ 200 g BW (P2), HFD group treated with Lakum leaf extract 40 mg/ 200 g BW (P3) and HFD group treated with simvastatin (P4).

poprotein secretion that can cause a decrease of cholesterol ester which is the main component of chylomicron and VLDL (Xenoulis & Steiner, 2010). Hyperlipidemia rats with simvastatin treatment (P4) have no significant difference with the control group. However, there is a significant difference with P1. Simvastatin is clinically proven to reduce cholesterol levels in the blood (Graveline, 2015). Simvastatin effectively inhibits the HMG Co-A reductase so that it prevents cholesterol synthesis in the liver. This enzyme converts 3-hydroxy-3-methyl-glutaryl-CoA (HMG Co-A) into mevalonic acid as the first precursor in cholesterol formation (Shilpa et al., 2016). The decrease of mevalonic acid synthesis can reduce cholesterol levels in the liver, so does in blood circulation (Gazzerro et al., 2012)

The effect of administration of Kersen juice and extract of Lakum leaf on increasing level of HDL shows significant differences between the control group (P0) and P1 (Table 1.). However, there is no significant difference between hyperlipidemia rats treated by Kersen juice (P2) and extract Lakum leaf (P3). Compared to P1, there is no significant difference in P2, but the difference is significantly seen in P3. The ability of extract Lakum leaf in increasing HDL levels is due to the presence of flavonoid constituents. Flavonoid increases the production of Apo-A1. Apo-A1 used as a cofactor for LCAT (Lecithin-Cholesterol-Acyltransferase) and as a ligand to interact with the lipoprotein receptor in HDL (Nguyen at al., 2008). Vitamin C also has a role in increasing HDL levels. Vitamin C acts as a laxative to elevate fecal disposal and lower the reabsorption of bile which can be converted into cholesterol (Sudargo et al., 2017). Hyperlipidemia rats treated with simvastatin (P4) is significantly different from the control group (P0). Simvastatin inhibits cholesterol synthesis in the liver so that SREBP (sterol regulatory element-binding protein) in the membrane is broken down and transported to the nucleus. Transcription factors then bind to the LDL receptor. The increase of LDL receptor in hepatocyte membrane reduces the cholesterol level and effects on the decrease of LDL, VLDL, and IDL level, and also elevate the level of HDL (Tripathi, 2013).

Administration of Kersen juice and extract of Lakum leaf in decreasing the level of LDL shows a significant difference between the control group (P0) and P1 (table 1.), but no significant difference between P2 and P3 compared to P0 and P1. Although none of the treatments can significantly reduce LDL levels, Kersen juice and Lakum leaf contain flavonoid which is potential in lowering LDL levels. Low-Density Lipoprotein (LDL) is a transport protein that carries triglyceride, cholesterol, and phospholipid from the liver to all tissues (Rajalakshmy, 2011). HFD consumption without consuming antihyperlipidemic agents automatically increases the cholesterol level in the blood, so does the LDL level (Marques et al., 2016). Flavonoids can increase the activity of lipoprotein lipase to inhibit cholesterol synthesis enzyme. This inhibition can increase the formation of the LDL receptor in the liver (Mahmood et al., 2014). Flavonoid also inhibits the synthesis of Apo B-48 and Apo B-100. The decrease of Apo B-48 and Apo B-100 can disturb the formation of chylomicron, VLDL, IDL, and LDL (Dashty, 2014). The use of simvastatin significantly reduces the level of LDL. Statistically, it shows that there is a significant difference between hyperlipidemia rats treated by simvastatin (P4) and control group (P0). Simvastatin inhibits HMG Co-A reductase which converts HMG Co-A into mevalonic acid as the precursor for the cholesterol biosynthesis. Cholesterol synthesis inhibition in the liver can reduce the LDL level in the plasma. Simvastatin also reduces LDL levels by increasing the number of LDL receptors. When cholesterol catabolism increases, it will lower the level of cholesterol and LDL (Graveline, 2015).

Administration of Kersen juice and extract of Lakum leaf in decreasing triglyceride level shows a significant difference between the control group (P0) and P1 (table 1.). The high level of triglycerides in P1 probably due to the consumption of HFD without any antihyperlipidemic agents. Triglycerides have the highest portion of the diet. When food is being digested, more calories needed by muscle cells. HFD consumption can increase the number of fat that will be deposited in adipose tissue. Overconsumption of HFD will not be used directly by the body but will be stored in adipose tissue as triglycerides. When the cells need energy, triglycerides will be hydrolyzed into free fatty acid and glycerol. This free fatty acid, later on, will be oxidized to produce energy (Kumar et al., 2013). Hyperlipidemia rats treated by Kersen juice (P2) and Lakum leaf extract are significantly different compared to the control group (P0). This result is related to the flavonoid that present in both Kersen and Lakum leaf. Flavonoid increases the activity of lipoprotein lipase and can affect the triglyceride level (Gross, 2004). Phenol is another constituent presents in both Kersen and Lakum leaf, which have an effect on decreasing the triglycerides level (Ragasa et al., 2014). Phenol decreases the secretion of lipopro-

Table 2. Rate of body weight and food consumption

Variables (g)	Treatment				
	P0	P1	P2	P3	P4
Food Consumption	$15.75^{a} \pm 0.5$	$11.25^{b} \pm 0.5$	$10.5^{b} \pm 1.29$	$10.75^{b} \pm 0.5$	$10.25^{b} \pm 1.5$
Body Weight	$290^{a} \pm 15.45$	$251.5^{b} \pm 21.14$	$222.7^{bc} \pm 18.62$	$226.7^{bc} \pm 26.32$	$208^{c} \pm 24.28^{c}$

Values are expressed as Mean ± SD, ^{abc}Different notation indicates $p<0.05$ using Duncan test, Normal control group (P0), HFD control group (P1), HFD group treated with Kersen juice 0.2 ml/ 200 g BW (P2), HFD group treated with Lakum leaf extract 40 mg/ 200 g BW (P3) and HFD group treated with simvastatin (P4).

tein in the liver and intestine, reduce cholesterol esterification process so that it reduces the level of cholesterol ester (Apro, 2015). Cholesterol ester is the main component of the formation of chylomicron and VLDL. Phenol inhibits the synthesis of Apo B-48 and Apo B-100 in the erythrocyte and liver. This inhibition decreases the formation of chylomicron, VLDL, IDL, and LDL and makes the level of triglycerides decrease (Mehta & Bhatt, 2017). In this study, the rates of body weight and food consumption have been investigated.

Based on data in Table 2, it was found that the food between the control group (P0) and the hyperlipidemia group (P1, P2, P3, P4) is significantly different. The highest food consumption rates are found to be a control group which is 15.72 g, whereas the food consumption rate for the hyperlipidemia group is 10.25 g. Statistically, there is no significant difference between hyperlipidemia rats treated by Kersen juice, Lakum leaf extract, and simvastatin.

HFD administered to the rats consists of 21.4 % lipid and 5% of alpha-cellulose. This composition could be a reason that makes the food consumption rates of hyperlipidemia rats was lower than the control group. Food consists of fibers that increase the viscosity through the formation of an impermeable gel layer along the gastrointestinal tract. The gel formation by fibers, block the contact between food and digestive tract which can affect the secretion of digestive enzymes and makes nutrients less absorption (Dhingra et al., 2012). The low food consumption rates in hyperlipidemia rats can be assumed that a HFD has already contained enough calories needed by the cell to perform. When the energy needs have been fulfilled, the breaking down of stored energy from protein and fats are no longer needed, as a consequence, food consumption rates will decrease (Wolfenshon & Lloyd, 2013). HFD administered to the rats also consists of choline chloride 0.25%. Choline chloride is an additive substance that can increase the efficiency of energy use both from carbohydrate and lipid catabolism to produce glucose. Choline acts as a methyl group donor in lipid catabolism to produce energy as well as a precursor in cholesterol and lipoprotein synthesis (Hesti et al. 2015)

Statistical analysis ($P<0,05$) on the body weight rates (table 2) showed that it is significantly different between the control group (P0) and hyperlipidemia group (P1, P2, P3, P4). However, there is no significant difference between hyperlipidemia groups, before and after treatments. Based on the data, the control group (P0) has the highest body weight rates which are 286.5 g. Meanwhile, hyperlipidemia groups have lower bodyweight rates. The HFD administered to the rats contains 20% of fructose and 21,4% oil. Paz-Filho et al, (2012) said that a high amount of energy storage in the cell could stimulate leptin hormone secretion by adipose cells which will send signal to the receptor in the hypothalamus to send "full" signal so that the food consumption will decrease. Appetite is regulated by the Leptin hormone. Facey at al (2017) said that high-fat diet consumption decreases more of the leptin hormone level than a high carbohydrate diet. The lower level of the leptin hormone will increase the appetite and the bodyweight will increase as well. These benefits of Lakum leaf and Kersen juice in increasing HDL and lowering cholesterol levels may become a promising alternative therapy solution for hyperlipidemia patients.

CONCLUSION

Administration of Lakum leaf extract significantly decreases the level of cholesterol and triglycerides, but not significantly decrease the level of HDL. However it increases the HDL level. The administration of Kersen juice significantly reduces the level of triglycerides but not significantly decrease the level of cholesterol, and not significantly increase the HDL level.

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