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Antihyperlipidemic Activity and HMG CoA Reductase Inhibition of Ethanolic Extract of *Zingiber Cassumunar* Roxb in Fructose-Induced Hyperlipidemic Wistar Rats*

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Abstract

HMG-CoA (3-hydroxyl-3-methyl-glutaryl-coenzyme A) reductase is a liver enzyme that plays an important role in the process of cholesterol synthesis in the liver. Statins are one of the major drug classes for lowering cholesterol through inhibition of HMG-CoA reductase enzyme activity. This study aims to determine the effect of *Zingiber cassumunar* Roxb ethanol extract as anti-hyperlipidemia and its effect on HMG-CoA reductase enzyme in the liver. A total of 30 white Wistar rats were grouped randomly into 6 groups: group 1 (receiving drug carrier), group 2 receiving drug carrier), group 3 (receiving simvastatin 0.9 mg / kg), group 4-5 (receiving extract dose 30, 50, and 100 mg / kg). All groups (except group 2) received 25% fructose in drinking water for 21 days. Day 22 was taken by blood for examination of total cholesterol, HDL, LDL, and triglyceride levels. Then the rats were sacrificed for liver organ isolation and made homogenate liver 20% for HMG CoA reductase enzyme activity test. The results showed that ethanol extract of *Zingiber cassumunar* Roxb dose 30, 50, and 100 mg / kg can decrease total cholesterol, triglyceride, LDL and increase HDL level compared to control group. Extracts of doses of 30, 50, and 100 mg / kg can inhibit the activity of HMG CoA reductase enzyme with a percentage of 11, 20, and 47% inhibition respectively. The results can be concluded that *Zingiber cassumunar* Roxb has anti-hyperlipidemia activity. One of the mechanisms of action is by inhibiting the activity of HMG CoA reductase enzyme.

Keywords: Fructose, HMG-CoA Reduktase, Hyperlipidemia, Simvastatin, *Zingiber cassumunar* Roxb

INTRODUCTION

Hyperlipidaemia is a condition in which total cholesterol increases, Low Density Lipoprotein (LDL) are high while High Density Lipoprotein (HDL) decreases, or a combination of these disorders [1]. Hyperlipidaemia is a major cause of coronary heart disease. An estimated 17.5 million people die from cardiovascular disease in 2012, with a percentage of 31% of all deaths in the world. The death, estimated at 7.4 million was due to coronary heart disease and 6.7 million was due to stroke [2]. In Indonesia the prevalence of coronary heart disease, heart failure, and stroke is seen to increase with the increasing age of respondents. The prevalence of stroke is similar in males and females [3].

Fructose is a sweetener widely used in various food and beverage products. The excessive use of fructose is reported to cause various health problems including hyperlipidemia. It has been proven by animal studies that 25% of fructose in drinks for 21 days significantly increased hyperlipidemia [3]. Mice receiving food containing 66% of fructose for 15 days experienced hypertension [4]. Fructose can also form acetyl-CoA used in fatty acid synthesis. High-fructose diets are reported to increase the risk of metabolic syndrome [5]. Metabolic syndrome is characterized by hyperglycemia, obesity, dyslipidemia (hypertriglyceride, decreased HDL, elevated cholesterol) and hypertension [6].

Drugs used to manage hyperlipidaemia are classified into five groups: Statin, Fibrat Acid, Resin, Nicotinic Acid (niacin) and Ezetimibe. Simvastatin is a statin agent that works inhibiting HMG-CoA reductase competitively on the process of cholesterol synthesis in the liver. This enzyme plays a role in converting acetyl CoA to mevalonate acid. But the side effects of using simvastatin as a blood cholesterol-lowering drug can lead to toxic myopathy [7]. Therefore, many hyperlipidemia patients prefer to use medicinal plants as an alternative therapy. This is an opportunity for research of natural materials that are considered more safe and efficacious in controlling and lowering cholesterol levels in the blood.

Zingiber Cassumunar Roxb is a plant that has long been used as a traditional medicine to cope with various diseases including hyperlipidemia. This rhizome, empirically used by the people in Indonesia to overcome fever, headache, cough sputum, colds, constipation, jaundice, worm infection, muscle aches and obesity [8].

Based on the above description, this study aimed to determine the antihiperlipidemia activity of ethanol extract from *Zingiber Cassumunar* Roxb rhizome and its effect on HMG CoA reductase enzyme activity that plays an important role in the synthesis of cholesterol in the liver.

MATERIALS AND METHODS

Plant Material

Rhizome of *Zingiber cassumunar* obtained from Manoko Lembang plantation, Bandung, West Java, Indonesia. Furthermore, botanical plant identification was done at the Laboratory of Plant Taxonomy Department of Biology, Padjadjaran University, Bandung (no. 121 / HB / 01/2016).

Extract Preparation

The fresh rhizomes are washed to be cleaned from impurities, then cut into small pieces and dried using 37ºC oven. Dry rhizome is made powder to facilitate the extraction process. Rhizome powder was extracted with 96% ethanol solvent for 3 days. The extraction results,

concentrated using a rotary evaporator at a temperature of 50-60^{o}C. Then, the extract was dried over water bath at 50-60^{o}C.

Screening of Phytochemistry Content

The dried extract, used for phytochemical screening and examination of the quality of the extract. Phytochemical screening was performed to determine the content of active compounds in the extracts including flavonoids, tannins, saponins, triterpenoids, and steroids. Extract quality checks include moisture content, total ash content, water soluble extract, and ethanol-soluble extract content.

Animals

This study was conducted on male Wistar rats, age 2 months, body weight 160-200 g. Animals adapted to laboratory conditions in enclosures with a light dark cycle of 12 hours, receiving standard food, drinking water ad libitum. The test protocol has been approved by the animal ethics committee, medical faculty, Padjadjaran University, Bandung, Indonesia (315 / UN6.C1.3.2 / KEPK / PN / 2016).

Study Design

A total of 30 male Wistar rats were divided randomly into 6 groups each 5 rats: group 1 (received drug carrier), group 2 (received drug carrier), group 3 (received simvastatin dose 0.9 mg / kg), group 4-6 received extract dose 30, 50, and 100 mg / kg. All groups (except group 2) received 25% fructose in drinking water for 21 days.

On the 22nd day, blood is taken to get serum. Serum is used for measurement of total cholesterol, LDL, HDL, and triglyceride levels. Total cholesterol and triglycerides were determined enzymatically using a reagent kit Proline®, while measurement of HDL and LDL cholesterol levels using a reagent kit Sekisui®. The color change in the sample was measured using a MicroLab 300® at a wavelength of 340 nm.

HMG CoA reductase Inhibitory Assay

Furthermore, animals were sacrificed and isolated liver and cleaned in 0.9% NaCl solution. The cleansed liver, homogenized 20% in phosphate buffer pH 7.4 and centrifuged at 8000 rpm, then supernatant separated (homogenate). Homogenate is used to test the activity of the HMG CoA reductase enzyme.

A 50 mL of liver homogenates, 260 mL of phosphate buffer pH 7.4, 42 mL of 50 mM Na 2 EDTA solution, 60 mL solution of dithiothreitol (DTT) 100 mM (purchased from Sigma), 50 mL of 2.16 M KCl solution, and 12 mL of HMG CoA substrate solution (purchased from Sigma) was mixed using a vortex for 10 seconds and incubated at 37 ° C for 30 minutes. After an incubation period, then added 55 mL of 1,105 mM NADPH (purchased from Sigma) and remixed using a vortex for 10 seconds and then incubated for 10 minutes. The absorbance of the sample were measured by MicroLab 300® at a wavelength of 340 nm.

Data Analysis

The data obtained were analyzed statistically using SPSS. Data are expressed as mean ± standard deviation. The p value <0.05 indicates a significant difference compare to control group.

RESULTS

The result of quality test of ethanol extract of *Zingiber cassumunar* rhizome was obtained ash content of 9,45%, 10% water content, water soluble content of 72,42% and soluble extract content of ethanol 87,69%. Water content in the extract should be no more than 10%, because water is a growth medium for microorganisms and also as a medium of enzymatic reactions that can decompose the active compound. The results of phytochemical screening, ethanol extract of *Zingiber cassumunar* rhizomes contain compounds: flavonoids, triterpenoids, tannins and steroids.

The results showed that administration of fructose 25% in drinking water for 21 days, increased total cholesterol, LDL, and triglyceride levels, and decreased HDL levels in the blood. Administration of *Zingiber cassumunar* ethanol extracts of 30, 50, and 100 mg / kg for 21 days can lower total cholesterol, LDL and triglyceride levels and increase HDL cholesterol levels (tables 1 and 2).

The group receiving the extract at a dose of 50 mg / kg showed a decrease in total cholesterol and LDL levels compared with those receiving 30 and 100 mg / kg extracts. However, the 30 and 100 mg / kg doses still showed a statistically significant decrease effect compared to group 1 ($p < 0.05$).

The group receiving 30 and 50 mg / kg dose extracts showed significantly different triglyceride levels statistically ($p < 0.05$) compared to group 1 (Table 1). The decreased triglyceride levels in the group receiving doses of 30 and 50 mg / kg were greater than those receiving the dose of 100 mg / kg. However, administration of the extract at a dose of 100 mg / kg can lower triglyceride levels by day 22 but not statistically significant ($p > 0.05$) compared to group 1 (table 1).

The dose of extracts of 50 and 100 mg / kg could increase statistically significant HDL levels ($p < 0.05$) compared to group 1 (table 2). The increase in HDL cholesterol levels at doses of 50 and 100 mg / kg was greater than the dose of 30 mg / kg. Administration of the extract at doses of 30 mg / kg can increase HDL cholesterol levels on day 22 but not statistically significant ($p > 0.05$) compared with group 1 (table 2).

The extract of doses of 30, 50 and 100 mg / kg for 21 days was able to inhibit the activity of the enzyme HMG CoA reductase in the liver. The inhibitory value of the enzyme activity of HMG CoA reductase was calculated as percent inhibition (table 4). The higher percent inhibition indicates the stronger the test drug inhibits the activity of the enzyme HMG CoA reductase.

Table 1. The Average Level of Total Cholesterol and Triglycerides Serum at Day 0 and Day 22 for All Treatment Groups

Group	TC ± SD (mg/dL)		TG ± SD (mg/dL)	
	T0	T22	T0	T22
1	67.5 ± 7.7	121.9 ± 6.8	83.0 ± 5.5	182.9 ± 29.8
2	59.5 ± 5.5	**68.3 ± 11.6***	83.0 ± 7.7	**93.1 ± 11.5***
3	64.4 ± 10.1	**84.2 ± 9.8***	83.2 ± 10.1	**117.0 ± 12.4***
4	62.8 ± 5.7	**100.0 ± 16.4***	84.6 ± 5.7	**148.4 ± 9.5***
5	63.2 ± 5.8	**86.9 ± 7.9***	83.7 ± 5.8	**129.8 ± 16.0***
6	69.9 ± 7.02	**93.3 ± 9.88***	83.6 ± 7.02	172.7 ± 24.0

Group 1: received drug carrier (CMC Na 1%) and 25% D-fructose
Group 2: received drug carrier (CMC Na 1%)
Group 3: received simvastatin 0.9 mg/kg orally
Group 4: received extract dose of 30 mg/kg and 25% D-fructose
Group 5: received extract dose of 50 mg/kg and 25% D-fructose
Group 6: received extract dose of 100 mg/kg and 25% D-fructose
*significant difference compared to group 1
($p<0.05$)

Table 2. The Average Level of Cholesterol LDL and Cholesterol HDL Serum at Day 0 and Day 22 for All Treatment Groups

Group	LDL ± SD (mg/dL)		HDL ± SD (mg/dL)	
	T0	T22	T0	T22
1	16.2 ± 2.2	79.0 ± 8.6	19.2 ± 2.7	6.2 ± 1.7
2	19.9 ± 2.7	**20,3 ± 1.5***	21.2 ± 2.6	**22.4 ± 3.9***
3	18.3 ± 2.0	**33.2 ± 4.2***	16.5 ± 13.0	**21.5 ± 5.1***
4	17.0 ± 2.8	**61.0 ± 3.4***	16.2 ± 13.0	10.3 ± 2.2
5	19.1 ± 3.0	**42.5 ± 8.0***	16.1 ± 3.2	**17.2 ± 4.3***
6	19.1 ± 4.0	**57.2 ± 6.0***	16.6 ± 4.0	**17.1 ± 4.3***

Group 1: received drug carrier (CMC Na 1%) and 25% D-fructose
Group 2: received drug carrier (CMC Na 1%)
Group 3: received simvastatin 0.9 mg/kg orally
Group 4: received extract dose of 30 mg/kg and 25% D-fructose
Group 5: received extract dose of 50 mg/kg and 25% D-fructose
Group 6: received extract dose of 100 mg/kg and 25% D-fructose
*significant difference compared to group 1
($p<0.05$)

Tabel 3. The Average Value of Absorbance in HMG CoA Reductase Assay for All Group of Treatment

Group	Absorbance ± Standard Deviation (SD)
1	0.115 ± 0.037
3	0.053 ± 0.031
4	0.102 ± 0.005
5	0.092 ± 0.020
6	0.061 ± 0.020

Group 1: received drug carrier (CMC Na 1%) and 25% D-fructose
Group 3: received simvastatin 0.9 mg/kg orally
Group 4: received extract dose of 30 mg/kg and 25% D-fructose
Group 5: received extract dose of 50 mg/kg and 25% D-fructose
Group 6: received extract dose of 100 mg/kg and 25% D-fructose

Table 4. The Percentage Inhibition of HMG-CoA Reductase Activity for All Treatment Groups

Group	Percentage Inhibition ± Standard Deviation (%)
3	53.9 ± 9.2
4	11.3 ± 8.6
5	20.0 ± 4.6
6	47.0 ± 4.6

Group 3: received simvastatin 0.9 mg/kg orally
Group 4: received extract dose of 30 mg/kg and 25% D-fructose
Group 5: received extract dose of 50 mg/kg and 25% D-fructose
Group 6: received extract dose of 100 mg/kg and 25% D-fructose

DISCUSSION

Study of the anti-hyperlipidemia activity of ethanolic extract of Zingiber cassumunar Roxb, aimed to test the ability of extract in improving lipid profile in animal models of fructose-induced hyperlipidemia. A diet of 25% fructose in drinking water for 21 days (with standard food) was able to raise total cholesterol and triglyceride levels more than twice their normal value, increasing LDL levels about 5 times their normal value, and being able to lower HDL levels 3 times its normal value. These results are in line with research conducted by R. Borate 2011, that the fructose diet increases total cholesterol, triglyceride, and LDL levels and decreases HDL [9]. Other studies also reported a high-fructose diet significantly increased the concentration of triglycerides and LDL cholesterol [10]. Studies on the women population in the US, reported that the fructose diet affects cardio metabolic biomarkers including lowering HDL cholesterol [11].

A 25% fructose diet in drinking water for 21 days can be used to make animal models of hyperlipidemia especially for studies that test the effects of the drug on LDL cholesterol levels. It is known that elevated levels of LDL cholesterol play a role in the process of atherosclerosis is the formation of foam cells in blood vessel endothelial cells that cause disruption of blood flow characterized by decreased elasticity of blood vessels (stiffness of blood vessels) [12].

Previous research has reported that a 25% fructose diet in drinking water in male Wistar rats can increase systolic and diastolic blood pressure and increase heart rate [13]. So a 25% fructose diet in 21 days can be used as an animal model with cardiovascular disorders. The mechanism of cardiovascular disorders is thought to occur through increased risk of atherosclerosis (elevated levels of oxidized LDL) [14], stiffness of blood vessels (increased systolic and diastolic blood pressure), and increased risk of heart failure (increase in heart rate) [15].

Although elevated levels of total cholesterol and a decrease in HDL cholesterol may increase the risk of cardiovascular disease, an increase in LDL cholesterol has been shown to have a very strong association with the risk of cardiovascular atherosclerosis [16]. Therefore, lowering LDL cholesterol levels is still the main therapeutic target for reducing the risk of cardiovascular disease [17]. Previous studies have shown that the risk of cardiovascular

atherosclerosis occurs in a population of patients who do not achieve target LDL cholesterol levels [18].

Statins have been shown to have good ability to lower LDL cholesterol levels [19]. Currently statins are still the main drug of choice for hyperlipidemia. The use of statins has been shown to decrease the occurrence of heart attacks and increase life expectancy in patients at high risk of cardiovascular attacks [20].

Atherosclerosis occurs through a complex process and a long time. The progression of atherosclerosis is influenced by various factors including genetic, risk factors and patient lifestyle [21]. However, heart attacks due to atherosclerotic plaque occur suddenly. Therefore, ideally, LDL-lowering cholesterol drugs are given early on before the formation of atherosclerotic plaque or early stage of atherosclerosis that can still be repaired. However, the difficulty of making animal models of atherosclerosis, as well as the many factors that affect the occurrence of atherosclerosis leads to limited studies of hyperlipidemia drugs. This poses a challenge for the study of non-invasive methods for early detection of atherosclerotic plaque, which begins with decreased elasticity of blood vessels [20].

However, the use of long-term statins requires monitoring of liver function and rhabdomyolysis side effects. This increases the risk of patient non-adherence to the therapy so that the patient does not achieve the therapeutic target [22]. This, the challenge as well as the opportunity of herbal medicine as a source of new drugs to lower cholesterol, especially LDL cholesterol.

Based on the results of this study has proven that ethanolic extract of *Zingiber cassumunar* can improve lipid profile in animal models of fructose-induced hyperlipidemia. The dose extract of 50 mg / kg was able to lower LDL -46% cholesterol, triglyceride -29%, total cholesterol -29% and increase HDL cholesterol 3 times (177%). The results of this study, reinforce previous research, that ethanolic extract of *Zingiber cassumunar* can decrease heart rate in animal models of 25% fructose induced arrhythmias in drinking water, thereby reducing the risk of heart failure [13].

Our study was able to demonstrate the effect of *Zingiber cassumunar* in increasing HDL cholesterol by 3-fold. This is an opportunity to develop the potential benefits of *Zingiber cassumunar* very strongly in increasing HDL cholesterol, in addition to lowering LDL cholesterol. Previous studies have reported that HDL cholesterol plays a role in the regression of atherosclerotic plaque by decreasing inflammatory factors [23]. Therefore, increasing HDL cholesterol levels are a potential therapeutic target as atheroprotection in patients with high cardiovascular risk [24].

A decrease in LDL cholesterol can occur due to inhibition of HMG CoA reductase in the liver. This enzyme plays an important role in regulating endogenous cholesterol synthesis. The body's need for cholesterol is largely supplied through endogenous synthesis in the liver. However, the presence of genetic abnormalities in the number of LDL receptors, hyperactivity of HMG CoA reductase enzyme, and the effect of dietary excess cholesterol, causes hyperlipidemia.

Our results showed that ethanolic extract of *Zingiber cassumunar* have the ability to inhibit the activity of the HMG-CoA reducing enzyme in the liver with increased inhibition percentage in accordance with increasing the dose of the extract. The percentage of inhibition obtained is used to calculate the IC50 value of the linear regression equation. The dose of *Zingiber cassumunar* extract which can inhibit 50% of HMg CoA reductase enzyme activity was 106 mg / kg.

HMG-CoA reductase is the rate-limiting enzyme of cholesterol synthesis in the liver. This enzyme as a catalyst in the cholesterol biosynthesis reaction. HMG CoA reductase is the target of statin drugs, as a competitive inhibitor of HMG CoA reductase enzyme activity . Statins bind to the active side of the HMG CoA reductase, thus inhibiting substrate access (HMG CoA) against the active site. While NADPH, as the second substrate of the enzyme, is not occupied by inhibitor molecules. As the effect of the reaction is decreased cholesterol synthesis in the liver so that cholesterol levels in blood decreases [25].

The results of phytochemical screening of ethanolic extract of *Zingiber cassumunar* showed the presence of secondary metabolite compounds including flavonoids and tannins. These results are in line with studies reporting that *Zingiber cassumunar* contains various bioactive compounds that have various pharmacological activities such as anti-inflammatory, antimicrobial, anticancer, antioxidant, antimalarial [26]. Flavonoids and tannins in *Zingiber cassumunar* are thought to be active compounds that act as inhibitors of HMG CoA reductase enzyme activity. However, it requires further research to prove it. Other studies have reported that the active compound in the ethanolic extract of *Zingiber cassumunar* has an anti-inflammatory effect [26].

CONCLUSION

The results of this study, it can be concluded that *Zingiber cassumunar* Roxb ethanol extract can show the activity of anti-hyperlipidemia in animal models of fructose-induced hyperlipidemia. One of the mechanisms of action of *Zingiber cassumunar* ethanol extract in lowering cholesterol through inhibition of HMG CoA reductase enzyme, an enzyme that plays an important role in the synthesis of endogenous cholesterol in the liver.

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