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Antihyperlipidemic, hepatoprotective and nephroprotective effects of functional beverages containing soybean (*Glycine max* L.), sweet potato leaves (*Ipomoea batatas* L.) and red yeast rice on a high fat diet-induced hyperlipidemia rats

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ABSTRACT

One of the primary risk factors for hyperlipidemia is an excessively high-fat diet. Due to their phytochemical composition and biological activity, red yeast rice (RYR), sweet potato (*Ipomoea batatas* L.) leaves and soybeans (*Glycine max* L.) are known to possess antihyperlipidemia and antioxidants effects. The purpose of this study is to ascertain how beverages containing soybeans, sweet potato leaves, and red yeast rice affect rats fed a high-fat diet in terms of hyperlipidemia, liver damage, and kidney damage. Five groups of rats were used: normal control, positive control using Commercial Smoothie Drink 1 (CSD1), 3.6 ml/day, negative control, and treatment groups receiving beverage doses of 1250 mg/kg and 2500 mg/kg respectively. Following the induction of the high-fat diet in the animals, functional beverage treatment was administered for 14 days starting on day 15 for a total of 28 days. The findings demonstrated that in rats fed a high-fat diet, the administration of functional beverages at a dose of 2500 mg/kg significantly (p<0.05) decreased serum levels of cholesterol, triglyceride, creatinine, blood urea nitrogen, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT). It is concluded that functional beverages may offer protection against hyperlipidemia, liver, and kidney damage caused by a high-fat diet.

Keywords: *Functional beverages; high fat diet; red yeast rice; sweet potato leaves and soybeans*

INTRODUCTION

Hyperlipidemia is condition of the body when low density lipoprotein (LDL), total cholesterol, triglycerides increase and blood levels of high density lipoprotein (HDL) decrease. According to Kementerian Kesehatan RI (2013) in Indonesia, 35.9% had cholesterol disorders, 15.9% had an increase in LDL, 11.9% had an increase in triglycerides, and 22.9% had low HDL. A high-fat diet in the long term can cause hyperlipidemia and increase the formation of reactive oxygen species (ROS) which will result in oxidative stress. Oxidative stress is a condition in which the production of free radicals exceeds the ability of intracellular antioxidants to neutralize them, thus potentially causing cell damage (Suarsana & Suprayogi, 2013). Oxidative damage caused by free radicals has implications for various pathological conditions, namely damage to cells, tissues, and organs in both humans and animals. This damage can end in cell death resulting in accelerated emergence of various degenerative disease (Halder & Bhattacharyya, 2014). Antioxidants can ward off free radicals and inhibit increased oxidative stress, because antioxidants can stabilize free radicals by working to complement the lack of electrons in free radicals and then inhibit the formation of free radicals by inhibiting chain reactions. There are many sources of natural antioxidants in foodstuffs which generally have antioxidant activity because these plants contain secondary metabolites or active compounds, including flavonoids, phenolics, tannins and anthocyanins (Fajriah Sofa, 2007).

Utilization of sweet potato leaves, soybeans and red yeast rice has been formulated into a functional beverages that has an effect as an antihyperlipidemic and antioxidant. Sweet potato contains quite high anthocyanin compounds, so it can have an effect improvement of blood lipid profile activity, lowering triglycerides, LDL, total cholesterol, and increased HDL cholesterol activity in male white rats given sweet potato leaf extract doses of 3 ml, 6 ml and 9 ml. Soybean contains phytoestrogens such as isoflavone daidzein (7,4'-trihydroxy isoflavone) and genistein (5,7,4'-trihydroxy isoflavone) and glycitein which is easily absorbed by the intestine and has the potential as a cholesterol-lowering agent due to the statin group which is a hypolipidemic by inhibiting the action of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG Co-A reductase).

This study aims to determine the effect of giving functional beverages made from sweet potato leaves (*Ipomoea batatas* L.), soybean (*Glycine max* L.) and red yeast rice against levels of cholesterol, triglycerides, blood urea nitrogen, creatinine, SGOT, SGPT and histopathological features of the liver in rats fed with high-fat diet.

METHODOLOGY

The research design used was a post-test-only control group design. Data collection was carried out after the experimental animal treatment, by comparing the data of the treatment group with the normal group. The independent variable in this study was the dose of a functional beverages made from sweet potato leaves (*Ipomoea batatas* L.), soybean (*Glycine max* L.) and red yeast rice. The dependent variables were the levels of cholesterol, triglycerides, blood urea nitrogen, creatinine, SGOT and SGPT. The controlled variables were strain, age and sex of the rats.

Preparation of functional beverages

The preparation of functional beverages involves multiple stages, including ingredients selection, washing, and processing the ingredients to become instant. Then the raw material formulation for making instant functional beverages for human consumption was prepared at ratio of 100 mg per 150 mL of water. The formulation of soybean, sweet potato leaves, and red yeast rice-based functional beverages was shown in Table 1.

Table 1

Composition of functional beverages containing soybean, sweet potato leaves and red yeast rice

Material	Weight (g)
Sweet potato leaves	3.36
Red yeast rice	1.2
Soya bean	20
Powdered skimmed milk	7
Powdered full cream milk	3
Sugar	15
Maltodextrin	7.2
Xhantan gum	2.5
Total	59.26

Test animals

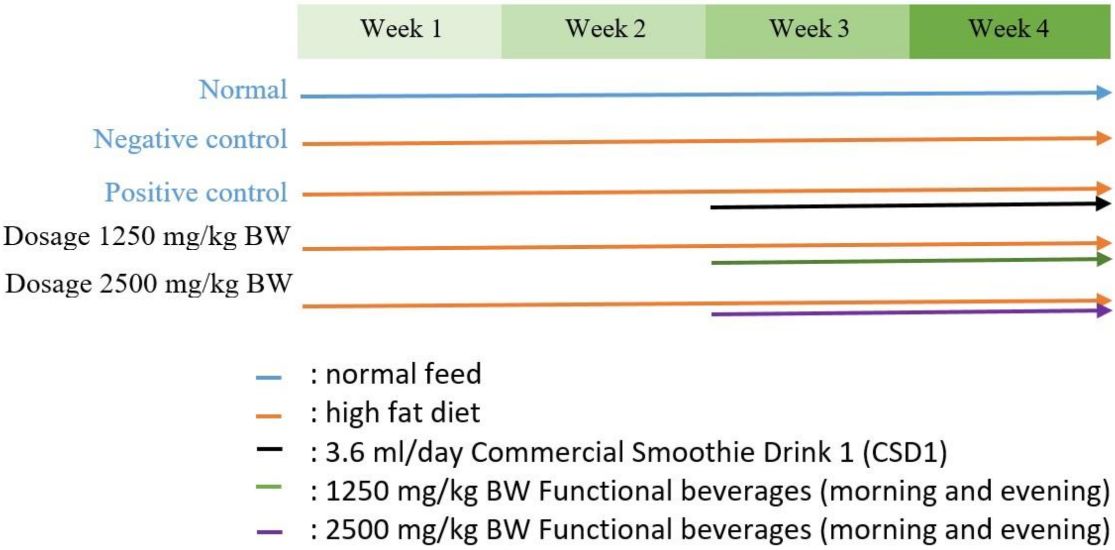
The test animals used were white *Rattus norvegicus* L. Wistar strain rats, males, 2-3 months old, and 150-250 gram body weight (BW), maintained in a room with sufficient dark-light cycle, sufficient ventilation, and maintained humidity. The test animals were acclimated for 7 days before starting to be treated. All treatments were carriedut by taking into account the welfare aspects of the test animals and obtaining ethical approval from the Universitas Ahmad Dahlan Research Ethics Committee number 012108049.

Hypercholesterol induction and experimental design

The study was conducted on 30 Wistar rats which were divided into 5 groups with each group consisting of 6 test animal per groups subjects based on Federer's formula calculations. The schedule treatment groups were presented in Figure 1.

Figure 1

Treatment schedule for the animal study



Note: BW = body weight.

Blood sample preparation

In this study, blood and liver samples were taken from the test animals on day 29. Blood samples were taken through the orbital sinus and centrifuged at 4000 rpm for 15 minutes to separate the serum and red blood. Serum samples were collected and analyzed for absorbance using a UV spectrophotometer with the Diasys reagent kit, following protocols provided by the kit manufacturer.

Measurement of cholesterol and triglyceride levels

Cholesterol levels were measured using the method enzymatic photometric test CHOD-PAP (Cholesterol oxidase-aminoantipyrin peroxidase). While the parameter of triglyceride levels used the enzymatic photometric test GPO-PAP (Glycerol-3 phosphate oxidase-phenol aminoantipyrin) method. The measurement of cholesterol levels were determined using the Diasys kit with UV-Vis spectrophotometry at a wavelength of 546 nm. Calculation of total cholesterol and triglyceride levels using the formula:

$$Ks = \frac{As}{Ast} \, x \, Kst$$

Information: Ks = Cholesterol/triglyceride level of sample (mg/dl)
Kst = Cholesterol / standard triglyceride levels (mg/dl)
As = Absorption in the sample
Ast = Absorption at standard

Measurement of SGOT and SGPT levels

Observation of SGOT and SGPT levels was carried out by kinetic method. The 100 µL of blood serum was mixed homogeneously with monoreagent (4 parts of reagent 1 and 1 part of reagent 2) of 1000 µL of ASAT (GOT), as well as observations of SGPT with ALAT reagent (GPT). Readings were taken using a UV spectrophotometer at a wavelength of 365 nm in photometric mode at 1, 2, 3, and 4 minutes. The assessment of SGOT and SGPT activity following treatment was conducted to determine the hepatoprotective effect, and this assessment was used to calculate the percentage reduction (Mahfudh et al., 2021) as follows:

$$\% \, Decrease = \frac{Mean \; value \; of \; SGOT \; or \; SGPT \; in \; the \; negative \; control \; group - Value \; of \; SGOT \; or \; SGPT \; in \; the \; treatment \; group}{Mean \; value \; of \; SGOT \; or \; SGPT \; in \; the \; negative \; control \; group} \; x \; 100\%$$

Measurement of BUN and creatinine levels

BUN levels were assessed using the GLDH (glutamate dehydrogenase) method, which is a fully enzymatic method. The Diasys reagent was used with kinetic measurements and carried out using the protocol as provided by the manufacturer. The reagents used in R1 were Tris buffer (pH 7.8), ADP, urease, 2-oxoglutarate and GLDH, while in R2 it was NADH. Measurements were made at a wavelength of 340 nm, temperature 37°C. BUN content calculation formula:

$$UREA \; (mg/dl) = \frac{Abs \; A1 - Abs \; A2}{A \; (Std/Cal)} \times conc \; Std/Cal \; (mg/dl)$$

$$BUN = Urea \; (mg/dl) \times 0.467$$

Creatinine levels were measured using the Jaffe method, a method without deproteination in the form of a photometric-colorimetric test for measurement kinetic. The reagent used is R1; sodium hydroxide 0.2 mol/L and R2; picric acid 20 mmol/L with creatinine standard 2 mg/dL. Creatinine will react with picric acid in alkaline conditions to form a yellow-orange complex. The intensity of the color formed is equivalent to the creatinine level in the sample. Measurements were made at a wavelength of 492 nm, temperature 37°C. The formula for calculating creatinine levels:

$$Creatinin \; (mg/dl) = \frac{abs \; A2 - abs \; A1}{A \; (Std/Cal)} \times conc \; Std/Cal \; (mg/dl)$$

Statistical analaysis

The average values of the calculated levels and activities were then statistically analysed using SPSS software. The first analysis is homogeneity test using Levene test and Shapiro Wilk normality test. Levels and activities were analyzed using the One Way ANOVA parametric test to determine whether there were differences between treatment groups and using the Tukey HSD test to test between groups. Levels and activity were also tested with Kruskal wallis to determine whether there was a difference in the average of the 5 groups and analyzed with the Mann Whitney test to test between groups.

RESULTS

Cholesterol and triglyceride levels

Measurement of cholesterol and triglyceride levels in functional beverages made from soybeans, sweet potato leaves, and red yeast rice showed significant results compared to the negative control group (p<0.05). The highest decrease occurred in the 2500 mg/dL dose group. The results of the posttest mean cholesterol levels after 28 days of treatment are presented in Table 2.

Creatinine and blood urea nitrogen (BUN) levels

The results of examining the average BUN levels after 28 days of treatment are presented in Table 3. The present study found that high fat diet treatment increase of creatinine level significantly shown the reducing of kidney function. The high concentration of lipid in the blood induce lipid accumulation in the kidney and followed renal function reduction. The oxidative stress resulted by high accumulation of lipid was suggested as mechanism (Gai et al., 2019; Sun et al., 2020). The creatinine level was found to decrease significantly after treatment with functional beverage. The BUN level was also increase following the HFD treatment and the treatment with 2500 mg/kg BW of functional beverages was effective in decreasing of BUN level.

SGOT and SGPT activities

Research result on the activity of SGOT and SGPT in rats that had been treated for 28 days can be seen in Table 4. The high fat diet treatment increase the SGOT and SGPT activities. The increasing of liver enzyme showed the decreasing of liver function (Giannini et al., 2005). The liver function amelioration was showed after treatment with functional beverage significantly (p<0.05). The percentage of hepatoprotection of functional beverages was shown in Table 5.

Table 2

Average of cholesterol and triglyceride levels of high fat diet rats treated by functional beverages containing soybean (Glycine max L.), sweet potato leaves (Ipomoea batatas L.) and red yeast rice

Group	Cholesterol level (mg/dL)	Triglyceride level (mg/dL)
Normal	45.76 ± 6.08 *^	58.18 ± 9.03 *
Positive control	102.46 ± 4.30 *#	60.32 ± 7.12 *
Negative control	147.38±10.29#^	169.84±6.99#^
Dosage 1250 mg/kg BW	67.02 ±10.11 *#^	51.76 ± 7.32 *
Dosage 2500 mg/kg BW	60.35 ±8.49 *#^	45.13 ± 8.12 *#^

*Note: * = significant difference with negative control (p<0.05), # = significant difference with normal control (p<0.05) and ^ = significant difference with positive control (p<0.05).*

Table 3

Average levels of creatinine and blood urea nitrogen of high fat diet rats treated by functional beverages containing soybean (Glycine max L.), sweet potato leaves (Ipomoea batatas L.) and red yeast rice

Group	Creatinine level (mg/dL)	BUN levels (mg/dL)
Normal	0.75 ± 0.12*	12.00 ± 0.60*
Negative control	1.86 ± 0.33^#	14.28 ± 0.38^#
Positive control	0.93 ± 0.36*	17.86 ± 1.12*#
Dosage 1250 mg/kg BW	1.20 ± 0.121*#^	17.12 ± 0.41*#
Dosage 2500 mg/kg BW	0.71 ± 0.18*^	13.64 ± 0.38*^

*Note: * = significant difference with negative control (p<0.05), # = significant difference with normal control (p<0.05) and ^ = significant difference with positive control (p<0.05).*

Table 4

SGOT and SGPT activities of high fat diet rats treated by functional beverages containing soybean (Glycine max L.), sweet potato leaves (Ipomoea batatas L.) and red yeast rice

Group	Activity average	
	SGOT±SD (U/L)	SGPT±SD (U/L)
Normal	84.54 ± 1.09*^	62.11±1.75*^
Positive control	76.78 ± 0,80*#	54.35 ± 1.09*#
Negative control	103.52 ±9.04#^	67.50 ±4.70#^
Dosage 1250 mg/kg BW	81.30 ± 1.61*#^	57.58 ± 1.46*#^
Dosage 2500 mg/kg BW	74.62 ± 1.97*^	49.60 ± 1.80*#^

*Note: * = significant difference with negative control (p<0.05), # = significant difference with normal control (p<0.05) and ^ = significant difference with positive control (p<0.05).*

Table 5

The percentage of hepatoprotection of functional beverages containing soybean (Glycine max L.), sweet potato leaves (Ipomoea batatas L.) and red yeast rice

Group	% reduction in activity	
	SGOT±SD (U/L)	SGPT±SD (U/L)
Normal	18.33 ± 1.18*	7.98 ± 2.90*
Positive Control	25.83 ± 0.87#	19.48 ± 1.82#
Dosage 1250 mg/kg BW	27.32 ± 1.74*#	14.69 ± 2.42*#
Dosage 2500 mg/kg BW	27.9 ± 2.13#	26.51 ± 2.98*#

*Note: * = significant difference with negative control (p<0.05) and # = significant difference with normal control (p<0.05).*

DISCUSSION

High fat diet will increase cholesterol and triglyceride levels. Increased levels of fat cause the formation of cholesterol. Later, cholesterol will be absorbed by the intestine and combined into chylomicrons. After chylomicrons release triglycerides in adipose tissue, the remaining chylomicrons will carry cholesterol to the liver. Most of the cholesterol in the liver will join the VLDL. This resulted in a high increase in VLDL. VLDL is a lipoprotein which is rich in triglycerides (Murray et al., 2009).

In the positive control group that was given the CSD1, it was shown to reduce cholesterol levels, according to the respective claim. A clinical trial conducted on the Indonesian population showed that CSD1 which contains plantstenol ester 1.7 gram plant stanol equivalent can significantly reduce total cholesterol and LDL cholesterol in people with high cholesterol levels (Lestiani et al., 2018).

In the group that was given a functional beverages made from soybeans, sweet potato leaves, and red yeast rice, doses of 1250 mg/kg and 2500 mg/kg showed a reduction in cholesterol and triglycerides with no significant difference between the two groups ($p>0.05$). This is in line with previous research which stated that sweet potato leaves can reduce cholesterol and triglyceride levels. Flavonoids in sweet potato leaves work by inhibiting cholesterol absorption in the intestine, increasing bile excretion and inhibiting HMG-CoA. The HMG-CoA reductase enzyme helps the HMG-CoA reaction to become mevalonate, so that the flavonoid will bind to the HMG-CoA reductase enzyme and cause the reaction not to occur. Flavonoids act as inhibitors which can cause reduced mevalonic acid (Lairin et al., 2016).

Flavonoid compounds such as quercetin and anthocyanins inhibit the activity of the acetyl-Co-A carboxylase enzyme, this enzyme functions in the synthesis of fatty acids which results in the synthesis of triglycerides being inhibited along with the enzyme diacylglycerol acyltransferase (DGAT). The inhibition of the DGAT enzyme led to the absence of conversion of 1,2-diacylglycerol into triglycerol or triglycerides. This inhibition, in turn, of triglyceride synthesis and resulting in decreased triglyceride levels. Red yeast rice contains Monacolin K which is produced by the fungus *Monascus sp*, monacolin K (statin) has structural homology with hydroxy acids and HMG-CoA so that it can inhibit the process of cholesterol biosynthesis through inhibition of the activity of the HMG-CoA reductase enzyme (Bunnoy et al., 2015). Red yeast rice is also known to be able to lower triglyceride levels by around 13 to 44%. The effect of flavonoids which are pigments produced by fermented red yeast rice on total cholesterol, triglyceride, HLD and LDL levels in the blood of male white rats is thought to increase the lipoprotein lipase enzyme compound which will increase VLDL catabolism (Wahid et al., 2019).

The decrease in total blood cholesterol levels that occurs is due to soybeans containing isoflavones consisting of genistein and daidzein. The content in soybeans can bind to blood lipid profiles resulting in decreased absorption of cholesterol and bile acids in the small intestine which causes increased fecal excretion of bile acids and steroids, the liver also converts more cholesterol in the body into bile which results in decreased cholesterol and increases LDL cholesterol receptor activity, followed by a decrease in cholesterol in the blood (Takahashi et al., 2005).

The significant difference between the normal group and the negative control group indicated that the test animals given a high-fat diet had hyperlipidemia and could trigger oxidative stress. This increase in creatinine levels indicates a kidney disorder, because creatinine should be filtered by the kidneys until the creatinine level reaches normal levels. Oxidative stress can also cause the severity of kidney damage due to free radicals. Excessive amounts around the kidneys can damage and even kill tubular and glomerular cells by taking one pair of electrons on the kidney cells (Mahfudh et al., 2021).

The positive control group showed that the kidney had improved. Giving CSD1 can lower cholesterol levels by reducing cholesterol absorption in the body. Provision of functional beverages made from soybeans, sweet potato leaves and red yeast rice acts as an antioxidant that stabilizes free radicals. It can be seen from the results of the analysis that showed no significant difference between the positive group given CSD1 and the treatment group at doses of 1250 mg/kg and 2500 mg/kg. At a dose of 2500 mg/kg the creatinine levels were not significantly different (p>0.05) from the normal group, but at a dose of 1250 mg/kg there was a significant difference (p<0.05) from the normal group.

Abnormal fat metabolism as a result of continuous administration of HFD can produce excessive free radicals that trigger liver tissue and cell disorders. Changes in cell permeability cause transaminase enzymes (SGOT and SGPT) to leave the cell and enter the cellblood vessels resulting in an increase in SGOT and SGPT enzymes in the blood (Anggraeny et al., 2021).

Plant stanol esters (PSE) contained in CSD1 was able to suppress cholesterol absorption in test animals, it can be seen in the decreased activity of SGOT and SGPT when compared to the negative group. A study shows that there is a relationship between increasing and decreasing cholesterol activity with increasing and decreasing SGOT and SGPT activities (Kurniati, 2012).

Decrease in SGOT and SGPT activity in the group treatment doses of 1250 mg/kg and 2500 mg/kg compared to the negative group showed that functional beverages made from soybeans, sweet potato leaves and red yeast rice (RYR) contain antioxidants that are able to work on the body's cells to stabilize free radicals by donating their hydrogen atoms or breaking reactions peroxy radical chain through a cleansing effect (scavenger) to control stress on body cells (Zakaria et al., 2016). The best decrease was shown in the 2500 mg/kg treatment group with significant differences in SGOT and SGPT activity compared to the negative group and SGOT activity which was not significantly different in the positive group.

CONCLUSION

Giving functional beverages made from soybean (*Glycine max* L.), sweet potato leaves (*Ipomoea batatas* L.), and red yeast rice were able to provide pharmacological effects on cholesterol, triglycerides, blood urea nitrogen, creatinine, SGOT and SGPT levels in mice treated with a high-fat diet. The most effective selected dose of this functional beverages is the dose of 2500 mg/kg.

AUTHOR CONTRIBUTIONS

Nurkhasanah Mahfudh was involved in the conceptualization, methodology, resources, writing-review, editing, supervision and funding acquisition. Atika Orchida Sari was involved in formal analysis, investigation, data curation and writing the original draft. Iradatul Ikhtiari was involved in formal analysis, investigation, data curation and writing the original draft. Nanik Sulistyani was involved in supervision and funding acquisition. Ika Dyah Kumalasari was involved in writing-review and editing, supervision and funding acquisition. Fezah Othman was involved in writing, reviewing and editing.

ETHICS APPROVAL

All treatments were carried out by taking into account the welfare aspects of the test animals and obtaining ethical approval from the Universitas Ahmad Dahlan Research Ethics Committee number 012108049.

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CONFLICTS OF INTEREST

All the authors declare no conflict of interest in this work.

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