Veriani Aprilia_macedonian

by Zee Zee

Submission date: 20-Jan-2022 12:29AM (UTC-0600)
Submission ID: 1744618968
File name: Veriani_Aprilia_macedonian.docx (81.6K)
Word count: 4388
Character count: 24665

The effect of Strobilanthes crispus on blood glucose levels and lipid profile of streptozotocin-induced diabetic rats

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Short title: *Strobilanthes crispus* effect on blood glucose levels and lipid profile

Funding: This research was supported by Universitas Alma Ata

The effect of *Strobilanthes crispus* on blood glucose levels and lipid profile of streptozotocin-induced diabetic rats

Abstract

BACKGROUND: Diabetes mellitus is a metabolic disease associated with unhealthy eating patterns, a lack of physical activity, obesity, smoking habits, and family history. *Strobilanthes crispus* (SC) contains antioxidant compounds known to exert a hypoglycemic effect during long-term interventions in non-diabetic samples.
AIMS: This study sought to determine the effect of administering the extract of SC leaves on the blood glucose levels and blood serum lipid profiles of streptozotocin (STZ)-induced diabetic rats.
METHODS: A total of 30 male *Rattus norvegicus* rats were divided into control and treatment groups. The control groups consisted of negative (normal rats) and positive controls (diabetic rats), whereas treatments groups consisted of diabetic rats administered with 3.2% and 16.8% SC leaf extract, and glibenclamide as the drug comparison groups. Blood samples were collected from the rats' retroorbital vein for the purposes of glucose level and lipid profile measurement before and after the induction of diabetes with STZ as well as 14 days after the intervention. The collected data were analyzed statistically by means of a one-way analysis of variance (ANOVA) continued with Duncan's multiple range test.
RESULTS: The results showed the rats to be hyperglycemic experienced changes in their lipid profiles following the induction of diabetes. The administration of 3.2% SC leaf extract for 14 days reduced the rats' blood glucose levels, while the effect of the 16.8% SC leaf extract was more pronounced in terms of reducing the rats' blood glucose levels and improving their lipid profiles (reducing the triglyceride, total cholesterol, and low-density lipoprotein cholesterol levels, while increasing the high-density lipoprotein cholesterol levels).
CONCLUSION: This study found 16.8% SC leaf extract to exert a good hypoglycemic effect and lead to an improvement in the lipid profiles in diabetic rats.

Keywords: *Diabetes mellitus, Strobilanthes crispus, blood sugar, lipid profile, rat*

Introduction

Diabetes mellitus (DM) comprises a group of metabolic diseases associated with defects in insulin secretion, insulin action, or a combination of the two (1). DM is currently the fourth leading cause of death worldwide (2). Among the different types of DM, type 2 DM is known to result from unhealthy eating habits, a lack of physical activity, obesity, smoking habits, and/or family history (3).

Hyperglycemia in patients with type 2 DM has been found to increase the formation of free radicals such as the superoxide, hydrogen peroxide, nitric oxide, and hydroxyl

radicals (4). Oxidative stress can result if the levels of free radicals exceed the antioxidants levels in the body, resulting in damage to the cell organelles and enzymes as well as increased lipid peroxidation. Increased levels of fat in the blood (dyslipidemia) serve as an indicator of the occurrence of lipid peroxidation (5). In addition, oxidative stress can also cause complications such as eye disorders, kidney damage, and nerve damage (6).

The consumption of antioxidants could inhibit the activity of free radicals. Keji beling (*Strobilanthes crispus* [SC]) is a local Indonesian plant species known for its bioactive properties, especially when it comes to treating diabetes and improving lipid profiles (i.e., polyphenols, alkaloids, coumarins, flavonoids, iridoids, triterpenes, and sterols) (7)(8). Several in vivo studies involving various doses and formulas of SC have demonstrated these beneficial effects. For example, a prior study found the ethanol extract of SC (a dose of 14.7 mg/g body weight [BW]) to be effective in terms of reducing the blood glucose levels in rats, although the results did not reveal a curative effect in DM subjects [9]. Other studies have examined the effect SC leaf juice administered at doses of 1 mL/kg BW, 1.5 mL/kg BW, and 2 mL/kg BW over a period of 30 days (9) (10) and in the form of ethanol extract administered at doses of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW over a period of 21 days (11). With regard to the safety of SC leaves, a toxicity analysis was only performed for 14 days of administration, although it revealed no instances of death and an no adverse effects on the liver and liver function (9,12). Longer toxicity analyses have not previously been performed, while only one long-term study of the glycemic effect of SC was identified in the literature (12). Thus, it is important to determine the glycemic effect of SC leaves over shorter periods (i.e., a maximum of 14 days).

The present study sought to determine the effect of SC leaf extract on the blood glucose levels and blood serum lipid profiles of streptozotocin (STZ)-induced diabetic rats after 14 days of treatment.

Materials and methods

Plant material and sample preparation

The SC leaves used in this study were obtained from Beringharjo Market, Yogyakarta, Indonesia. The leaf extract was made by macerating 3.2 g or 16.8 g of dried leaves in 100 mL of water for 24 hours. The liquid part was then separated from the residue by means of decantation.

Experimental animals

The protocol for this study was approved by the Health Research Ethics Committee of Universitas Alma Ata (Ref No: KE/AA/V/600/EC/2018). Male *Rattus norvegicus* rats weighing 185–224 g were used in this study. The rats were housed individually in an ambient condition with a 12 h light–dark cycle. The rats were fed AIN-93 diets (13) and given free access to drinking water. The rats' food intake and BW were recorded during the study.

Induction of diabetes and treatment

Thirty rats were divided into five groups, namely the normal/non-diabetic control group (negative control [NC] group), STZ-induced diabetic control group (positive control [PC] group), STZ-induced diabetic treated with 5 mg/kg BW glibenclamide group (GB group), STZ-induced diabetic treated with 3.2% SC leaf extract group (SC1 group), and STZ-induced diabetic treated with 16.8% SC leaf extract group (SC2 group). The positive control and diabetic treated groups were intraperitoneally injected with 110 mg/kg BW nicotinamide dissolved in 0.9% NaCl buffer saline prior to the injection of a single dose of 45 mg/kg BW STZ dissolved in citrate buffer to induce diabetes (14). The rats' diabetes status was determined on the third day following the STZ injection. All samples were administered orally as a single dose each day throughout the 14-day treatment period.

Blood sampling and biochemical analysis

Blood samples were collected from the rats' retroorbital vein by means of the microcapillary technique and then centrifuged at 400 rpm for 15 minutes to obtain the plasma. The rats' blood glucose levels and lipid profiles were measured three times, namely before and three days after the induction of diabetes as well as at the end of the intervention period. Rats with blood glucose levels up to 200 mg/dL were included in the diabetic groups. The utilized enzymatic assessment methods were glucose oxidase–peroxidase aminoantypirin (GOD-PAP) for the glucose levels, glycerol phosphate oxidase–phenyl aminophyrazolon (GPO-PAP) for the triglyceride levels, and cholesterol oxidase–peroxidase aminoantypirin (CHOD-PAP) for the cholesterol levels (total cholesterol, high density lipoprotein [HDL], and low-density lipoprotein [LDL]).

Statistical analysis

Data were performed as mean±standard deviation (SD) and analyzed by one-way analysis of variance (ANOVA) continued with Duncan's Multiple Range Test (DMRT) at $p<0.05$. The analysis used statistical package for the social sciences (SPSS) software (version 16.0 SPSS Inc., Chicago, USA).

Results

Feed intake and body weight of rat

Feed intake of rats during 14 days of treatment tended to be stable and began to increase at the end period of the study (Figure 1). All treatment groups showed an increase in body weight, except PC (Figure 2), This indicated that the treatment of GB, SC1, and SC2 were able to reduce the effect of weight loss experienced by diabetic rats (PC).

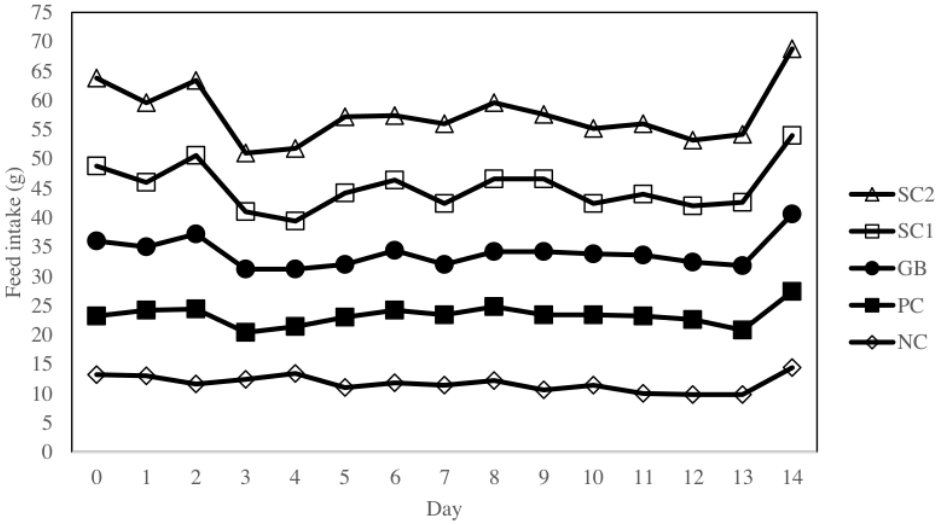

Figure 1: Feed intake of rats during 14 days of intervention. Control groups (non diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus leaf extract*/SC1,16.8% SC2)

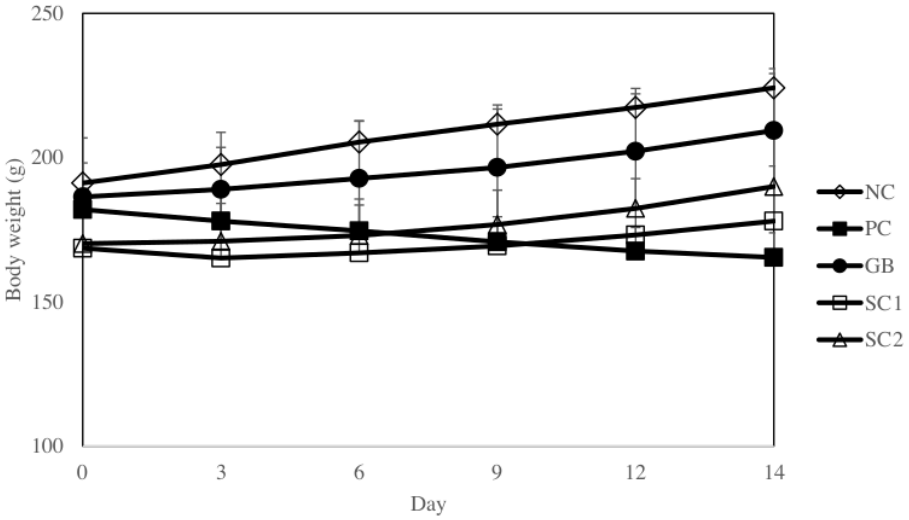

Figure 2: Bodyweight of rats during 14 days of intervention. Control groups (non- diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus leaf extract*/SC1,16.8% SC2)

Effect of SC on blood glucose levels

Table 1: Effect of various treatments on blood glucose levels of rats

Groups	Blood glucose levels (mg/dL)			ΔK
	Before STZ induction	After STZ induction (0 d)	After intervention (14 d)	
NC	68.5±2.9[a]	69.8±2.3[a]	71.3±2.1*	+1.50[b]
PC	68.7±3.0[a]	260.0±5.0[b]	260.9±5.0*	+0.83[b]
GB	69.9±2.6[a]	254.7±5.7[b]	97.0±1.3*	-157.66[a]
SC1	68.4±2.1[a]	256.5±5.9[b]	133.6±3.5*	-122.93[a]
SC2	69.8±2.6[a]	257.6±3.6[b]	109.0±1.4*	-148.6[a]

*) Significantly different between 0 d and 14 d using T-test. Superscript values in the same column are significantly different ($p < 0.05$) using one-way ANOVA followed by multiple comparison Duncan's test. ΔK with – and + values show the decrease and increase of blood glucose levels between 0 d and 14 d of intervention, respectively. Control groups (non diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus* extract/SC1,16.8% SC2)

It can be seen from Table 1 that the initial blood glucose level of rats was normal, at 68.4-69.9 mg/dL ($p>0.05$). Except for NC, almost all treatment groups were given STZ to significantly increase blood glucose levels ($p<0.05$). After 14 d of treatment, the blood glucose levels of GB, SC1, and SC2 groups were significantly lower than that of day 0 ($p<0.05$). At the same time, in the PC (positive control) group, blood glucose levels increased. It was proved that SC has the same effect as the commercially available drug group, and the effective lowering level of blood glucose levels was 3.2% for 14 d of treatment.

Effect of SC on lipid profile

Before STZ administration, the plasma triglyceride levels of rats in all treatment groups were normal, between 74.5-76.6 mg/dL. Administering STZ to the diabetic group (PC, GB, SC1, and SC2) had an impact in increasing triglyceride levels in the range of 126.6-129.4 mg/dL. The GB and SC2 interventions were able to significantly reduced blood triglyceride levels with a decrease of 29.23 and 20.45 mg/dL, respectively ($p<0.05$) (Table 2).

Table 2: Effect of various treatments on triglyceride levels of rats

Groups	Trygliceride levels (mg/dL)			ΔK
	Before STZ induction	After STZ induction (0 d)	After intervention (14 d)	
NC	76.6±2.5[a]	78.2±2.0[a]	81.9±1.9*	+3.74[d]
PC	75.2±2.7[a]	126.6±3.6[b]	127.9±3.6*	+1.33[d]
GB	74.5±2.0[a]	127.0±3.6[b]	97.9±2.5*	-29.23[a]
SC1	74.6±2.5[a]	129.4±1.5[b]	127.6±2.2	-1.86[c]
SC2	76.0±3.1[a]	128.4±3.2[b]	107.1±2.5*	-20.45[b]

*) Significantly different between 0 d and 14 d using T-test. Superscript values in the same column are significantly different ($p < 0.05$) using one-way ANOVA followed by multiple comparison Duncan's test. ΔK with – and + values show the decrease and increase of blood glucose levels between 0 d and 14 d of intervention, respectively. Control groups (non diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus* extract/SC1,16.8% SC2)

Table 3 shows that the total cholesterol levels in all treatment groups were the same, which was between 94-95.4 mg/dL. The presence of STZ induction in the diabetic rat groups significantly increased total cholesterol levels ($p<0.05$). SC was equivalent to GB in reducing the level of total cholesterol, the best concentration was 16.8% (SC2 group) ($p<0.05$).

Table 3: Effect of various treatments on total cholesterol levels of rats

Groups	Total cholesterol levels (mg/dL)			ΔK
	Before STZ induction	After STZ induction (0 d)	After intervention (14 d)	
NC	94.0±2.9[a]	94.9±2.6[a]	95.7±2.7	+0.75[c]
PC	94.4±1.4[a]	170.5±3.5[b]	174.4±4.2	+3.86[c]
GB	95.4±2.2[a]	177.5±5.1[c]	128.5±2.1*	-49.07[a]
SC1	95.2±2.7[a]	181.0±5.2[c]	156.8±1.87*	-24.20[b]
SC2	94.4±3.6[a]	180.2±7.7[c]	138.4±2.6*	-41.72[a]

*) Significantly different between 0 d and 14 d using T-test. Superscript values in the same column are significantly different ($p < 0.05$) using one-way ANOVA followed by multiple comparison Duncan's test. ΔK with – and + values show the decrease and increase of blood glucose levels between 0 d and 14 d of intervention, respectively. Control groups (non diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus* extract/SC1,16.8% SC2)

LDL cholesterol levels were in the range of 22.4-26.3 mg/dL which belonged to normal category. After being induced, LDL levels in diabetic rats increased and were significantly different compared to the normal rats' group (NC) ($p<0.05$). The 14-day intervention in the treatment group significantly reduced LDL cholesterol levels ($p<0.05$), while the untreated diabetes group (PC) did not. SC2 group had the highest reduction of cholesterol level with the same result with GB in the end of study (Table 4).

Table 4: Effect of various treatments on LDL cholesterol levels of rats

Groups	LDL cholesterol levels (mg/dL)			ΔK
	Before STZ induction	After STZ induction (0 d)	After intervention (14 d)	
NC	25.7±1.13[b]	25.2±1.12[a]	27,5±1.28*	+6.9[c]
PC	26.3 ±1.09[b]	73.4±2.56[c]	74.5±1.71	+1.1[c]
GB	25.2 ±1.43[b]	70.2±2.09[b]	33.4±1.55*	-36.8[a]
SC1	24.4 ±1.02[a]	75.7±1.75[c]	51.9±1.55*	-23.7[b]
SC2	22.4±2.47[a]	75.3±1.46[c]	38.4±3.11*	-36.9[a]

*) Significantly different between 0 d and 14 d using T-test. Superscript values in the same column are significantly different (p< 0.05) using one-way ANOVA followed by multiple comparison Duncan's test. ΔK with – and + values show the decrease and increase of blood glucose levels between 0 d and 14 d of intervention, respectively. Control groups (non diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus* extract/SC1,16.8% *S.crispus* extract/SC2)

The HDL cholesterol levels of all groups were classified as normal rats at the beginning of the study and ranged from 80.8-82 mg/dL. STZ induced a reduction in HDL levels. Treatments for 14 d increased HDL levels significantly ($p<0.05$) with the same increasing effect in all groups of rats ($p>0.05$). Administering SC at a minimum level (3.2%) was able to give the effect of increasing HDL levels which was equivalent to the commercial drug group (GB) (Table 5).

Table 5: Effect of various treatments on HDL cholesterol levels of rats

Groups	HDL cholesterol levels (mg/dL)			ΔK
	Before STZ induction	After STZ induction (0 d)	After intervention (14 d)	
NC	81.9±1.41[a]	80.1±1.33[b]	79.5±0.99	+1.10[a]
PC	81.6±1.07 [a]	25.3±1.43[a]	25.1±1.20	-0,14 [a]
GB	82.0±1.41 [a]	25.1±0.38[a]	68.5±1.46*	36.01[b]
SC1	80.8±2.17 [a]	25.3±0.79[a]	49.4±1.82*	24.14 [b]
SC2	81.6±1.55 [a]	24.1±1.62[a]	62.5±2.08*	41.90[b]

*) Significantly different between 0 d and 14 d using T-test. Superscript values in the same column are significantly different (p< 0.05) using one-way ANOVA followed by multiple comparison Duncan's test. ΔK with – and + values show the decrease and increase of blood glucose levels between 0 d and 14 d of intervention, respectively. Control groups (non-diabetic rat/NC and STZ-induced diabetic rat/PC), treatment groups (STZ-induced diabetic rats treated with 5 mg/kg BW of glibenclamide/GB, 3.2% *S.crispus* extract/SC1,16.8% SC2)

Discussion

Feed intake and bodyweight of rat

In this study, SC treatment did not affect the rats' feed intake, which proved that there was no effect of SC administration on the rats' appetite. During the 14 days of treatment, the weight of rats that received SC intervention also increased a lot, while the weight of untreated diabetic rats (PC) continued to drop. Weight loss in diabetic rats was caused by

continual fat catabolism to meet energy needs in their body as a result of the inability of cells to metabolize glucose in the blood. This inability of glucose metabolism could be caused by a disruption of pancreatic -cells in producing insulin (15).

Effect of SC on blood glucose levels

The blood glucose levels of rats at the beginning of the study were categorized as normal, then significantly increased to >126 mg/dL or classified as high (16) after STZ induction. STZ inducted DM by donating NO (nitric oxide) which contributed to pancreatic cell damage by increasing the activity of guanyl cyclase and formation of cGMP. NO was produced when STZ led to metabolism in cells. In addition, STZ was also able to generate reactive oxygen, which had a high role in pancreatic cell damage (17). In a previous study, the inducement of diabetic by STZ influenced disorientation of liver cellular structures, including glycogen deposition, nuclear location on the periphery of cell membranes, and acidophilic cytoplasm. Liver cell also experienced to necroticization, microvascular vacuolization, and hydropic inflammation (18).

In this study, indications of DM in rats could also be observed from the higher urinary frequency (polyuria). In general, people with diabetes have symptoms of polyuria (a lot of urination), polydipsia (a lot of drinking) and polyphagia (a lot of eating) with weight loss (19). SC treatment was able to significantly reduced blood glucose levels in rats and was comparable to the drug (GB group) ($p<0.05$). These results were in line with previous study which showed that SC was effective in reducing blood glucose levels by giving the treatment at the dose of 14.7 mg/30g BW (20). In another study, processing SC into fermented tea also showed a decrease in blood glucose levels (10). This could be affected by the flavonoid content in SC which was able to act as an antioxidant by protecting pancreatic cell damage from the effects of free radicals, resulting in higher insulin sensitivity (21)(22). In addition, the antioxidant had the role in accelerating the release of glucose from the circulation which can reduce blood glucose levels (23).

Effect of SC on lipid profile

The lipid profile of rat at the beginning study including triglyceride, HDL, and LDL levels was normal (24)(25)(26), except total cholesterol level which was classified as high because the level was above 10-54 mg/dL (27). The presence of STZ induction changed the lipid profile to abnormal. As previously discussed, STZ was able to induce an increase in blood glucose levels (Table 1). It could be caused by insulin resistance affecting its fat metabolism (28). As a result of insulin resistance, sensitive hormone in adipose tissue increased, generated higher lipolysis of triglycerides in adipose tissue, leading to enhancement of free fatty acid levels in the blood. The excess of free fatty acids were converted into phospholipids, cholesterol, and some were used as raw materials for triglycerides generation in the liver which can then be transported into the blood in the form of lipoproteins (29). In this condition, abnormalities of fat metabolism occurred in the form of increased triglyceride levels, decreased HDL, increased small dense LDL subtraction, known as the atherogenic lipoprotein phenotype or lipid trial (30). Therefore,

the increase of blood glucose levels in DM patients had a significant correlation with the increase in triglyceride and cholesterol levels.

Administering SC for 14 days had a significant effect in improving lipid profiles. This can be seen from the SC's ability to significantly reduce triglyceride levels at a dose of 16.8% (SC2 group) and total cholesterol or LDL levels at a dose of 3.2% (SC1 group) ($p<0.05$). However, by administering SC at a dose of 16.8%, the best reduction in total cholesterol and LDL cholesterol levels was achieved or equivalent to commercial drugs. HDL cholesterol levels can be increased to normal and equivalent to commercial drugs starting from the SC dose of 3.2% ($p<0.05$).

This study was supported by previous experiment that using SC in the form of fermented tea which also showed improvements in lipid profiles such as lowering cholesterol, triglyceride, and LDL levels, but increasing HDL levels. In the form of SC ethanol extract at a dose of 400 mg/kg BW for 21 days of treatment, there was also a decrease in cholesterol and LDL levels (11). SC contains bioactive compounds such as alkaloids, saponins, β-sitosterol, flavonoids, tannins, potassium, and polyphenols. β-sitosterol was a hypocholesterolemic substance that might reduce cholesterol levels in the blood (10). The presence of β-sitosterol and flavonoids controlled cholesterol synthesis by inhibiting the activity of the enzyme acyl-CoA cholesterol acyl transferase (ACAT) in HepG2 cells which play a role in reducing cholesterol esterification in the intestine and liver. It also inhibited the activity of the HMG-CoA enzyme leading to inhibition of cholesterol synthesis (31). Flavonoids in SC reduced blood cholesterol levels by reducing or inhibiting the absorption of bile acids and cholesterol in the small intestine. It resulted in high excretion through feces leading to the formation of bile acids from cholesterol of liver cells. Increased excretion of fecal cholesterol also occurred because of the binding in the intestine between fiber with cholesterol and bile acids which will eventually be excreted or excreted through the feces. This reduced enterohepatic circulation of bile acids and increase the conversion of cholesterol into bile acids leading yo the decrease of plasma cholesterol levels (32).

Conclusions

This study proved that SC extract provided good hypoglycemic effect starting at a concentration of 3.2%. However, administration of 16.8% SC was optimal not only in lowering blood glucose levels, but improving lipid profiles in the form of decreasing levels of triglycerides, total cholesterol, LDL cholesterol, and increasing HDL cholesterol.

Acknowledgments

The authors would like to thank Alma Ata University for the many facilities for this study.

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