The supplementation effect of Red Dragon fruit's skin extract on the fasting blood glucose and lipid profiles in male Wistar rats with diabetes mellitus and dyslipidemia

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Abstract

Background. Flavonoids, saponins, tannins, phenols, and vitamin-C contained in the Red Dragon fruit's skin have a positive impact on glycemic control and lipid oxidation. This study aimed to determine the effect of Red Dragon fruit's skin extract on reducing the fasting blood glucose (FBG) and improving the lipid profile of Wistar rats with diabetes and dyslipidemia.

Methods. A randomized pre-test post-test control group experimental study was done on 22 male Wistar rats, aged 2-3 months that suffered from diabetes and dyslipidemia. Subjects were divided into the control group (given 2cc distilled water + 9 mg metformin) and the treatment group (given 160 mg red dragon fruit's skin extract + 9 mg metformin) for 14 days. FBG and lipid profile measurements were done before and after the treatment. Data were analyzed using the compare mean test.

Results. There was no significant mean difference of FBG between groups before ($p=0.414$) and after treatment ($p=0.125$), total cholesterol between groups before ($p=0.572$) and after treatment ($p=0.361$), triglycerides between groups before ($p=0.073$) and after treatment ($p=0.111$). There was a significant mean difference of HDL between groups before ($p=0.003$) and after treatment ($p=0.047$), LDL between groups before ($p=0.006$) and after treatment ($p=0.043$). Although there were significant mean differences in HDL and LDL between groups before and after treatment, the pre-post treatment of HDL and LDL mean differences showed no significant mean difference ($p=0.328$ and $p=0.704$ consecutively).

Conclusion. Red Dragon fruit's skin extract treatment did not significantly reduce the mean FBG and lipid profile levels.

Keywords: Diabetes, Dyslipidemia, Cholesterol, Red Dragon fruit's skin

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Introduction

According to the International Diabetes Federation (IDF), there were 415 million adults between the ages of 20 and 79 who experienced diabetes mellitus (DM) in 2015.¹ In 2018, there were 8.5% of people who suffered from DM in Indonesia. This number increased from the

previous data in 2013, which amounted to 6.9%.² DM is associated with an increased risk of cardiovascular disease. The state of dyslipidemia often occurs in DM which is referred to as a state of diabetic dyslipidemia. DM patients with dyslipidemia experience an increase in triglyceride and LDL levels and a decrease in HDL cholesterol levels.³ Patients with DM can experience the process of glycolyzing LDL cholesterol, thus LDL molecules are more easily oxidized and more easily to experienced the process of atherosclerotic plaque formation in the blood vessels.⁴

Controlled LDL cholesterol levels in the blood can reduce the emergence of heart and vascular disease.⁵ Just controlling the blood glucose levels in DM patients is not enough to prevent the deterioration of cardiovascular risk, because atherosclerotic plaque formation has occurred since the prediabetes phase. A 1% reduction in LDL cholesterol levels can reduce cardiovascular diseases risk by 1%, and a 1% increase in HDL cholesterol levels can reduce cardiovascular disease risk by 3%. The goal of therapy for LDL cholesterol in DM patients is < 100 mg/dL. Meanwhile, DM patients who are accompanied by cardiovascular disease are < 70 mg/dL.⁶

The non-pharmacological intervention, such as the regulation of diet and exercise, is the first-line therapy of diabetic dyslipidemia and is used in conjunction with pharmacological therapy. The 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitor drugs or also known as statins are a class of drugs that have been considered as the most effective drugs in treating dyslipidemia.⁷ However, the patient's non-compliance and discontinuation of statin consumptions are common due to statin-associated muscle symptoms (SAMS) side effects on muscles.⁸

Mostly, only the flesh part of the Dragon fruit is consumed, while the skin of the fruit is removed. Red Dragon fruit is easy to find in tropical countries, including Indonesia. The Red Dragon fruit's skin has a volume of approximately 22% of the total fruit. The previous study has mentioned the content of Red Dragon fruit's skin extract, which contains vitamin C, vitamin E, vitamin A, flavonoids, and polyphenols.⁹ Elvina and Martha found in their study that the steeping of Red Dragon fruit's skin can improve the blood glucose levels. Another study showed that the Red Dragon fruit's skin powder treatment per-orally for 30-days could improve the dyslipidemia conditions in rats.¹⁰

Vitamin E has a role as an antioxidant and contributes to increased insulin action by inhibiting protein kinase C. Vitamin E can reduce the levels of free radicals that cause oxidative stress, thus improving the insulin sensitivity.¹¹ The content of vitamin C in the Red

Dragon fruit's skin extract is 3,413.79 mg/100g. Vitamin C can improve the function of pancreatic β cells and can prevent a decrease in the mass of pancreatic β cells. Vitamin C also plays a role in increasing the insulin secretion in DM patients.¹² Vitamin C also plays a significant role in improving the condition of high total cholesterol and triglyceride levels.¹³

Flavonoids contained in the Red Dragon fruit's skin can prevent phosphodiesterase which caused an increased adenosine monophosphate (AMP) in pancreatic β cells, which can stimulate protein kinase A for the secretion of the insulin hormone.¹⁴ One type of flavonoid, quercetin, can balance blood glucose levels by inhibiting intestinal glucose absorption, increase the use of glucose in peripheral tissues, and increase insulin secretion from the pancreas.¹⁵ Flavonoids in Red Dragon fruit's skin can increase the activity of the lipoprotein lipase enzyme and can inhibit HDL damage, thus it can improve dyslipidemia conditions.¹⁶ Phenolic compounds contained in Red Dragon fruit's skin can prevent the LDL oxidation and can inhibit the cholesterol absorption in the intestine. In addition, phenol can also inhibit the activity of the HMG-CoA reductase enzyme.¹⁷ The saponin contained in the Red Dragon fruit's skin can inhibit the reabsorption of bile acids by intestinal cells, thus bile acids can be excreted immediately with faeces. So that cholesterol in the blood will be converted by the liver into bile acids, and a decrease in blood cholesterol levels will occur.¹⁸

Not many people in Indonesia know the benefits of Red Dragon fruit's skin for health. The unused skin part of the Red Dragon fruit turns out to has several nutrients that are better than the flesh of the fruit. Based on this, this study was conducted to assess the benefits of Red Dragon fruit's skin as an alternative therapy to reduce the blood glucose levels and improve the lipid profiles.

Method

Study design and samples

A randomized pre-test post-test control group experimental study was done on 22 male Wistar rats (*Rattus norvegicus*), aged 2 to 3-months with a bodyweight of 180-200 grams. The sample size of 24 Wistar rats as the research subjects was calculated using the Pocock formula. Samples that meet the requirements were taken randomly and divided into two groups, namely the control group and the treatment group.

Preparation

Wistar rats were adapted for one week and then given standard feed (594 pellets) and a high cholesterol diet with a composition of duck

egg yolk (5%) and lard (15%) for 30 days for the induction of dyslipidemia.¹⁹ Wistar rats that experienced dyslipidemia were defined as the Wistar rats with total cholesterol levels ≥ 200 mg/dL, then given a single dose injection of 13 mg/200 g body weight streptozotocin intraperitoneally. After 5-days of observation, all of the Wistar rats's blood samples were taken as many as 1 ml from the medial canthus sinus orbitalis to assess the FBG, total cholesterol, LDL, HDL, and triglyceride levels before treatment (pre-test). Red dragon fruit's skin extract is made using Red Dragon fruits obtained from the Dragon Fruit Garden in Badung, Bali.

Intervention

Each of the Wistar rat in the control group was given a placebo in the form of 2 ml distilled water and 9 mg metformin per day. At the same time, each of the Wistar rat in the treatment group was given a 160 mg dose of Red Dragon fruit's skin extract and 9 mg metformin per day. The intervention was diluted with distilled water up to a volume of 2 ml and given using a gastric feeding tube once a day every morning for 14 days. After the treatment was completed, the Wistar rats fasted for 8-hours, and then the blood samples were taken in the morning to measure the post-test FBG, total cholesterol, LDL, HDL, and triglycerides levels.

Data analysis

A compare mean test using the paired T-test was performed to compare the pre-test and post-test data in each group. While the compare mean test between the treatment and control group was performed using the independent T-test. All procedures in the study have been approved by the Ethics Committee – Faculty of Medicine, Udayana University, with the ethical clearance number #1072/UN14.2.2.VII.14/LT/2020.

Results

There were two samples that did not meet the DM criteria from a total of 24 Wistar rats, one in the control group and one in the study group. Thus, the total subjects analyzed in this study were 11 samples in each group. From the descriptive data shown in Table 1, there was a consistently decreased mean of FBG, total cholesterol, LDL, and triglycerides levels in the post-test control and treatment groups compared to the pre-test results. The treatment group also had a lower post-test mean of FBG, total cholesterol, LDL, and triglycerides levels compared to the control group. There were also increased mean of HDL levels in the post-test results of both groups compared to the pre-test results.

The pre and post-test FBG mean comparison test as well as the mean comparison between groups were presented in Table 1. The results of the pre and post-test comparison test showed significant mean differences in the control ($p < 0.001$) and treatment groups ($p < 0.001$). But, the results of compare mean test between the two groups did not show a significant mean difference in both pre-test ($p = 0.414$) and post-test ($p = 0.125$).

Table 1. The compare mean results of FBG and lipid profile between the control and treatment groups pre-test and post-test

Variable	Group	Pre-test	Post-test	$\Delta(\text{Pre-Post})$	p^{**}
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Fasting blood glucose (mg/dL)	Control	165.7 $\pm$ 20.6	117.9 $\pm$ 19.6	47.82 $\pm$ 30.02	<0.001
	Treatment	174.3 $\pm$ 26.9	106.5 $\pm$ 12.9	67.73 $\pm$ 24.46	<0.001
	p^*	0.414	0.125	0.104	
Total cholesterol (mg/dL)	Control	215.7 $\pm$ 9.70	191.7 $\pm$ 14.9	24.0 $\pm$ 20.60	0.003
	Treatment	213.3 $\pm$ 10.3	186 $\pm$ 13.8	27.3 $\pm$ 20.3	0.001
	p^*	0.572	0.361	0.711	
High density lipoprotein (mg/dL)	Control	40.5 $\pm$ 3.20	48.9 $\pm$ 3.50	8.50 $\pm$ 5.10	< 0.001
	Treatment	45.8 $\pm$ 4.30	52.4 $\pm$ 4.10	6.50 $\pm$ 3.70	< 0.001
	p^*	0.003	0.047	0.328	
Low Density lipoprotein (mg/dL)	Control	152.3 $\pm$ 4.5	128.8 $\pm$ 10	23.4 $\pm$ 11.1	< 0.001
	Treatment	139.9 $\pm$ 11.7	118.3 $\pm$ 12.6	21.6 $\pm$ 11.0	< 0.001
	p^*	0.006	0.043	0.704	
Triglycerida (mg/dl)	Control	163.8 $\pm$ 6.4	143.5 $\pm$ 16.7	20.4 $\pm$ 15.9	0.002
	Treatment	156.2 $\pm$ 11.5	132.6 $\pm$ 13.5	23.5 $\pm$ 14.5	< 0.001
	p^*	0.073	0.111	0.630	

p^* analyzed by independent T-test; p^{**} analyzed by paired T-test

The compare mean tests for total cholesterol, LDL, HDL and triglycerides levels were also shown in Table 1. The results showed that there were significant mean differences between the pre and post-test of the total cholesterol levels in the control ($p = 0.003$) and treatment groups ($p = 0.001$), HDL levels in the control ($p < 0.001$) and treatment groups ($p < 0.001$), LDL levels in the control ($p < 0.001$) and treatment groups ($p < 0.001$), and triglycerides levels in the control ($p = 0.002$) and treatment groups ($p < 0.001$). The compare mean test results between the two groups showed that there was no significant mean difference in the total cholesterol between the two groups pre-test ($p = 0.572$) and post-test ($p = 0.361$), and triglycerides levels between the two groups pre-test ($p = 0.073$) and post-test ($p = 0.111$). There were significant mean difference in the HDL levels between the two groups pre-test ($p = 0.003$) and post-test ($p = 0.047$), and LDL levels between the two groups pre-test ($p = 0.006$) and post-test ($p = 0.043$). Although there were significant HDL and LDL levels mean difference in the two groups pre-test and post-test, the pre-post difference (Δ) of mean HDL and LDL levels between the two groups showed no significant

difference (with Δ pre-post HDL $p = 0.328$; and Δ pre-post LDL $p = 0.704$).

Discussion

Various medicinal plants have been shown to improve DM conditions. The medicinal plants based on how it works in the treatment of DM were divided into 5 groups, namely by improving insulin resistance, improving pancreatic beta-cell function, regulating the balance of GLP-1, inhibiting the alpha-glucosidase enzyme, and having multiple actions.²⁰ The reducing FBG levels effect from the Red Dragon fruit's skin extract is influenced by various active compounds found in the skin of Red Dragon fruit, i.e. fiber, flavonoids, saponins, tannins, vitamin C, and vitamin E.

The compare mean test of FBG levels between the two groups showed no significant FBG levels mean difference between the treatment and control groups, even though the mean FBG levels reduction in the treatment group was greater. The mean reduction of FBG levels in the treatment group was 67.73 (38.86%) compared to the mean reduction of FBG levels in the control group was 47.82 (28.85%). These results were slightly different from the previous study conducted by Hastuti *et al.*, (2018) which found that the treatment of Red Dragon fruit's skin extract at a dose of 500 mg/kg BW reduced the mean blood glucose level by 53.28%.²¹ These results may be occurred due to more complex metabolic conditions in Wistar rats with the DM and dyslipidemia state, thus a larger extract dose and a longer study time range is needed. Giving a high-fat diet causes dyslipidemia conditions which can lead to insulin resistance due to an increase of the gluconeogenesis process and the occurrence of insulin resistance in the tissues. In DM patients, there is not only an increase of fasting blood glucose levels, but also lipotoxicity conditions can arise due to the high levels of free fatty acids in the blood which cause the hyperglycemia condition to get worse.²¹ In this study, it was also not certainly known which active components cause the reduction of FBG levels because the active component was not extracted.

The compare mean test results of total cholesterol and triglyceride levels between the two groups also showed that there was no significant difference between the treatment and control groups, although the mean reduction was higher in the treatment group. The decreased mean of total cholesterol in the treatment group was 12.8%, compared to the control group was 11.13%. The mean reduction of triglyceride levels in the treatment group was 15.08% compared to the control group was 12.43%.

The compare mean test results of HDL and LDL levels between

the two groups showed that there were significant differences between the treatment group and the control group at each of the pre-test and post-test, but there was no significant mean difference in the Δ pre-post between the treatment and control groups. The mean increase of HDL levels in the control group was higher (20.89%) than the mean increase in the treatment group (14.30%). The reduction of mean LDL levels in the control group was also higher compared to the treatment group.

These results were in contrast to the previous study conducted by Fatimah *et al.*, (2018) which found that the administration of Red Dragon fruit's skin extract of 160 mg/200g BW increased the HDL levels of rats with dyslipidemia by 64.6 mg/dL and decreased the LDL levels by 144.8 mg/dL.²² A previous study conducted by Fadlilah and Martha (2016) also found that that administration of Red Dragon fruit's skin steeping increased the HDL levels of rats that had dyslipidemia in its blood by 25.2%.²³

There were some limitations in this study. The treatment's time range carried out in this study was only for 14-days, where the ideal treatment's time range for a study to determine the changes in lipid profiles should be carried out for at least 3-months. The examination of blood glucose using the FBG levels did not represent the true blood sugar control. It is better to monitor blood glucose using the glycated albumin or HbA1c tests. Glycated albumin may reflect a longer blood glucose control up to 2-4 weeks earlier, while the HbA1c up to 3-months. HbA1c can provide a reflection of the blood glucose concentration from 3-months earlier. HbA1c examination is also not affected by food intake before the blood draw procedure. In this study, it was not certainly known which components of the active substances that cause improvements in FBG levels and lipid profiles. Due to the limitations of the extract's phytochemical examination facilities, it was only possible to determine the antioxidant ability.

Flavonoids, vitamin C, tannins, saponins, and fiber content in the Dragon Fruit's skins made it possible to improve the lipid metabolism in this study. Flavonoids and vitamin C can increase the HDL levels by stimulating the activity of the enzyme Lecithin Cholesterol Acyl Transferase (LCAT). LCAT is an enzyme that converts free cholesterol into ester cholesterol.²³ Cholesterol esters will form HDL by bonding with lipoprotein core particles. Tannins can reduce the cholesterol levels in the blood by inhibiting the fat absorption in the intestine and accelerating the elimination of cholesterol through faeces.²⁴ Saponins form a complex with cholesterol derived from the diet, which can reduce the blood triglyceride levels and inhibit the activity of the pancreatic lipase enzyme, so that the absorption of fat in the digestive tract is inhibited.²⁵ The fiber content can bind with the

fatty acids, bile acids, and cholesterol in the digestive tract so that fat cannot be absorbed and moving to the large intestine to be excreted through faeces.²⁶

In general, the studies that assess the changing metabolic parameters require a long intervention time. Previous studies by Weta *et al.*, on obese young women with a low ratio of n-6:n-3 fatty acids intervention for 12 weeks, found that there was a significant inhibition of increased FBG, and significantly decreased triglycerides and liver steatosis.^{27,28} The insignificant results in this study could be caused by several reasons. First, the intervention time range was too short (only 2-weeks). Second, the effect of the intervention was dominated by metformin as the preferred therapy for DM, thus the combination treatment's effect with Red Dragon fruit's skin extract was not clear. Third, it was possible that the dose of the Red Dragon fruit's skin extract used in this study was less than optimal. Considering these limitations, further research is needed to clarify the effect of Red Dragon fruit's skin extract.

Conclusion

Red Dragon fruit's skin extract treatment did not significantly reduce the mean FBG and lipid profile levels.

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