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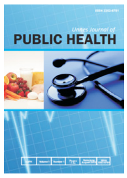

A New Opportunity Related Hypercholesterolemic and the Improvement of Glucose Levels, Lipid Profiles, and Microbial Activity: Red Dragon Fruit *(Hylocereus polyrhizus)* Peel Yogurt and Animal Study

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Abstract

Hypercholesterolemia estimated to cause 2.6 million deaths and 29.7 million disability problems. The incidence of Noncommunicable diseases (NCD) such as coronary heart disease (CHD), type 2 diabetes, and some types of cancer can be involved with hypercholesterolemiaed. Red dragon fruit (Hylocereus polyrhizus) peel contains total phenolic compounds, flavonoids and dietary fiber. Red dragon fruit (Hylocereus polyrhizus) peel, which was originally considered as trash can be used to produce yogurt. This study aimed to analyse the effect of red dragon fruit (Hylocereus polyrhizus) peel yogurt on levels of fasting blood glucose, lipid profile and microbial activity in hypercholesterolemic Wistar rats. This was an experimental- research with pre and post-test control group design. A total of 25 male Wistar rats were divided into five groups randomly. Hypercholesterolemic conditions in the Wistar rats were obtained from consuming solution consisted of 1% of cholesterol powder and 0.5% of cholic acid for 14 days. Each Wistar rats received 20 g/day standard feed. The grouping were Group 1 (negative control group); Group 2 (hypercholesterolemic group); Group 3 (1.8 ml/kg b.wt/day of dragon fruit peel yogurt); Group 4 (2.7 ml/kg b.wt/day of dragon fruit peel yogurt); Group 5 (3.6 ml/kg b.wt/day of dragon fruit peel yogurt). The intervention was performed for 28 days. Blood glucose levels and lipid profiles were measured before and after the intervention. Blood glucose, lipid profiles and microbial activity were measured using GOD-PAP, automatic biochemistry analyser and pour plate method respectively. Data were analysed using paired t test and one-way ANOVA. Blood glucose, TC, LDL-C, TG levels were decreased, and the other side HDL-C was increased significantly in the Group dragon fruit peel. There was no difference in the total number of microbes in all groups. Dragon fruit peel yogurt is effective in improving glucose levels and lipid profile of hypercholesterolemic Wistar rats.

INTRODUCTION

Hypercholesterolemia well known with elevated cholesterol levels. Hypercholesterolemia estimated to cause 2.6 million deaths and 29.7 million disability problems. The incidence of Noncommunicable diseases (NCD) such as Coronary Heart Disease (CHD), type 2 diabetes, and some types of cancer can be involved with hypercholesterolemia. Food intake is an important part of nutrition (Sivamaruthi et al., 2019). Risk factors associated with NCD manifestations can be prevented and improved through nutritio-

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nal therapy as a non-pharmacological therapy. One of the nutritional therapies to prevent and improve the risk factors for metabolic syndrome and various NCD are to consume probiotics, prebiotics and symbiotics (Mozaffarian, 2019).

Engineering of symbiotic product that are widely used are those from fruit and milk. Probiotic bacteria and food fiber which are classified as prebiotic can be processed into symbiotic products which have potential as functional food. Food products can be classified as functional food if they can affect a person's health condition. The potential of food as functional food can be seen from its antioxidant content. Food products containing probiotics in sufficient doses can change the intestinal microflora and play a role as antioxidant. In the digestive system from the mouth to the colon, microbiota can be found, both facultative and strict anaerobes, including Streptococci, Bacteroides, Lactobacilli and yeasts. The intestinal microbiota contains a large number of enzymes that can modify the components of food before they enter the colon. Microbial enzymes found in the colon can eliminate glycosides, glucuronides and sulphates, and produce flavonoid aglycons (Murota et al., 2018). Total plate count is one way to determine the interaction between bacteria and the host. The bacteria has a multicellular and cooperative behaviour (Ayala et al., 2017).

Research conducted on Americans and Koreans has shown that fruit and dairy products can lower the risk of blood pressure and metabolic syndrome (M. Fernandez & Marette, 2017). Dietary fiber which is classified as prebiotic plays a role for stimulating growth and probiotic activity, and also has bio-functionality in improving intestinal health and immunity, lowering blood pressure and cholesterol levels, and even reducing the risk of inflammation (Mofid et al., 2019). Red dragon fruit (Hylocereus polyrhizus) is widely researched and developed because it contains antioxidants, antimicrobials, antidiabetic and anticancer properties (Joshi & Prabhakar, 2020). Varieties of dragon fruit that have red flesh and peel, are oval in shape and have a sour to sweet taste are classified as red dragon fruit (Hylocereus polyrhizus). Nutritional and mineral content such as vitamins B1, B2, B3, C, protein, fat, carbohydrates, crude fiber, niacin, flavonoids, phenolics, betacyanins, lycopene, polyphenols and phytoalbumin are found in red dragon fruit (Hylocereus polyrhizus) (Choo, KY et al., 2018). Red dragon fruit (Hylocereus polyrhizus) waste that is underutilized is the peel. The weight of the red dragon fruit (Hylocereus polyrhizus) peel reaches 33 % of the total weight of red dragon fruit (Hylocereus polyrhizus) (Song, Chu, Xu et al., 2016). Betacyanins pigments can be found in red dragon fruit (Hylocereus polyrhizus) peel. Betacyanins (betanine, isobetanine, phyllocactin, isophyllocactin, betanidine, isobetanidin, hylocerenin) are identified as the main purplish red pigment. Other components that can be found in the peel are pectins, triterpenoids and steroids. Red dragon fruit (Hylocereus polyrhizus) peel contains phenolic compounds, antioxidant activity and higher food fiber than its flesh. Its high antioxidant activity has the potential to be developed as a natural antioxidant and even as a functional food.

The lack of knowledge about the management of red dragon fruit (Hylocereus polyrhizus) peel is one of the reasons for conducting this research. The management of red dragon fruit (Hylocereus polyrhizus) peel that has not been maximised has consequences for the increase in red dragon fruit (Hylocereus polyrhizus) peel waste. Red dragon fruit (Hylocereus polyrhizus) peel can be processed into yogurt. It is possible for the food industry to have an economic advantage by converting fruit waste into valuable materials. Dragon fruit peel yogurt is an alternative of fermented beverage processing to improve its product shelf life and marketability. The process of making red dragon fruit (Hylocereus polyrhizus) peel yogurt can be done at the household level and is expected to provide additional income for the family. Sources of animal protein, calcium, niacin, magnesium, and vitamin B-12 which play a role in improving nutrient absorption as well as digestion are some of the benefits of yogurt. A meta-analysis using 125 research articles showed that yogurt consumption can reduce total cholesterol dan triglyceride levels and increase HDLc (Shidfar F, et al., 2020).

This study aimed to determine the potential of red dragon fruit (Hylocereus polyrhizus) peel yogurt as an alternative to functional beverages on improvement blood glucose, lipid profiles and microbial activity in hypercholesterolemic Wistar rats.

METHOD

Animals and Diets

The facilities and handling of experimental animals during the study were carried out in compliance with the Guidelines for Care and Use of Laboratory Animals of CNFS Gadjah Mada University and were approved by the Committee on the Ethics of Health, Universitas Negeri Semarang (permission number: 140/KEPK/EC/2019). The Wistar rats were obtained from

House of Experimental Rats CNFS, Gajah Mada University, Yogyakarta, Indonesia. The inclusion criteria were male Wistar rats aged 8-12 weeks, weighed 150-240 grams with fasting blood glucose levels <110 mg/dL, healthy and had no physical abnormalities, active during the adaptation period and had no weight loss during the study of >10%. Wistar rats will be expelled if they die during the intervention period. In this study, no rats died due to the effect of treatment.

A dark/light cycle with a ratio of 12:12 hours and temperature of 25±1°C were applied to the cage environment to maintain normal room humidity. Cleaning and sanitation of the cage was carried out daily to minimize stress during the study. Each Wistar rat was placed in individual cages made of stainless steel and given 20 g/day standard feed with ad libitum water access. The Wistar rats were also acclimatised for seven days before receiving intervention.

Induction of Hypercholesterolemia

Hypercholesterolemic conditions in the Wistar rats were obtained from consuming solution consisted of 1% of cholesterol powder and 0.5% of cholic acid for 14 days (Atwaa et al., 2023). The feeding process was done using single intraperitoneal injection. The cholesterol and cholic acid powder were obtained from Sigma Aldrich, Japan.

Experimental Design

A total of 25 Wistar rats were divided randomly into five groups with five Wistar rats in each group (n = 5)(Charan & Kantharia, 2013). The groups include G1 (negative control group/did not receive treatment); G2 (positive control group/hypercholesterolemic rats); and three group was given red dragon fruit peel yogurt. G3 (hypercholesterolemic rats treated with red dragon fruit (Hylocereus polyrhizus) peel yogurt 1.8 ml/kg b.wt./day); G4 (hypercholesterolemic rats treated with red dragon fruit (Hylocereus polyrhizus) peel yogurt 2.7 ml/kg b.wt/day); G5 (hypercholesterolemic rats treated with red dragon fruit (Hylocereus polyrhizus) peel yogurt 3.6 ml/kg b.wt/day). The yogurts were administered 1x/day for 28 days orally by gastric intubation. The red dragon fruit (Hylocereus polyrhizus) peel yogurts were produced based on a research by Mardiana (Mardiana et al., 2020) and Putriningtyas (Putriningtyas & Wahyuningsih, 2017). The composition yogurt are milk:red dragon fruit (Hylocereus polyrhizus) peel:sugar:lactic acid bacteria (75% : 25% : 10 % : 5% Streptococcus thermophilus : 5% Lactobacillus bacilus) The rats body weight was monitored weekly and after 28 days, the rats were sacrificed by cervical decapitation. The body weight was measured using a static weight (Biosep-In Vivo Research Instrument, USA). The rats will be burned in the incinerator as the final stage of the research. Blood samples used for measuring fasting blood glucose levels, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were collected before and after the study, while the caecum data were collected only at the end of the study. This caecum data aims to determine the microbial activity in the digestion of Wistar rats.

Parameters Analyzed

Whole blood samples were obtained from retroorbital vein and centrifuged at 3000 rpm for 15 minutes to obtain blood serum before and after the study. Blood samples were obtained after fasting the rats for 8 hours. Fasting blood glucose levels were measured by the GOD-PAP (Glucose Oxidase Phenol 4- Aminophenazone) method, while levels of TC, LDL-C, HDL-C and TG were measured using an automatic biochemistry analyzer with standard kits following the manufacturer's instructions. Microbial activity was measured at the end of the study from the rats' faeces collected from the caecum. The total plate count was obtained using the pour plate technique on plate count agar or standard method agar. Each group was diluted with peptone solution and then 1 ml of each dilution was used for microbial count determination. The plates were inverted and incubated at 35±1oC for 48 hours. Duplicates were done for each dilution. The number of microorganism was expressed as colony-forming units per 1 gram of sample. The total plate count method used refers to the conventional method.

Statistical Analysis

The data of each group was shown as mean ± standard deviation (SD). Paired t test was used to determine the differences of each group before and after treatment. One-way analysis of variance (ANOVA) was used to determine differences in all groups and continued with the Bonferroni post hoc test to determine differences between groups. Values were considered statistically significant when $p<0.05$.

RESULT AND DISCUSION

The content of red dragon fruit (Hylocereus polyrhizus) peel yogurt (/100 mL) used in this study are water 80.65%; fat 2.11%; protein 2%; flavonoid 16.60%; non soluble fiber 2.44%; soluble fiber 0.05%; dietary fiber 2.49%. Red dragon fruit (Hylocereus polyrhizus) peel is a source of phenolics antioxidant due to its flavonoids content. Flavonoids are known as phenolic compounds that function as antioxidants. Water-based dragon fruit peel extract has a more attractive color with better antioxidant activity. Total phenolics content in dragon fruit peel extract dissolved using ethanol and water was in the range of 1.193 ± 0.011-1.351 ± 0.021 μg/mL (Hakim BNA et al, 2019). Lactic acid bacteria which are used for the fermentation process of milk can increase the nutritional content of yogurt, such as vitamins and phenols. Lactic acid bacteria can maximally grow and carry out fermentation activities by utilizing sugars or carbohydrates in the media to form lactic acid and results in a decrease in pH (Habib et al., 2019). The body weight can be seen in Table 1.

Table 1. Mean levels of body weight in wistars rats

Group	**Body weight (gram)**				
	Post hypercholesterolemia (mean±SD)	**Pre (mean±SD)**	**Post (mean±SD)**	**Δ (mean±SD)**	**p***
G1[a]	197.60±4.16	204.40±4.67	228.60±5.41	24.20±1.30	0.001
G2[b]	187.00±4.30	197.60±5.27	233.00±4.53	35.40±1.14[a]	0.001
G3[c]	189.60±6.27	200.20±7.36	225.80±7.86	25.60±0.55[b]	0.001
G4[d]	190.20±5.22	199.80±4.92	224.20±4.32	24.40±1.67[b]	0.001
G5[e]	200.00±4.06	210.20±5.36	235.40±5.46	25.20±3.49[b]	0.001

Sampling was done 14 days after induction of hypercholesterolemia and 28 days after start of treatment; G1: did not receive treatment; G2: Hypercholesterolemic; G3: Hypercholesterolemic, treated red dragon fruit peel yogurt 1.8 ml/kg b.wt/day; G4: Hypercholesterolemic, treated dragon fruit peel yogurt 2.7 ml/kg b.wt/day; G5: Hypercholesterolemic, treated red dragon fruit peel yogurt 3.6 ml/kg b.wt/day. Values represent the mean ± SD for observation mode on five rats in each group. Statistical analysis: p; paired t- test, significant difference (p<0.05); One-way analysis for variance (ANOVA), where significant, post hoc testing (least significant difference) was done for intergroup comparisons. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol
[a]Statistically significant difference (p<0.05) when compared with G1 values
[b]Statistically significant difference (p<0.05) when compared with G2 values
[c]Statistically significant difference (p<0.05) when compared with G3 values
[d]Statistically significant difference (p<0.05) when compared with G4 values

The data analysis results showed that there were significant differences in each group during the study (p<0.05). The body weight of Wistar rats in all groups increased during the study period. The weight gain in the group that received dragon fruit peel yogurt (G3; G4; G5) was not as high as the weight gain in the positive control group. This is possible because of the natural anti-obesity effect of red dragon fruit (Hylocereus polyrhizus) peel yogurt. Soluble and insoluble fiber with a ratio of 1.0:3.8 were found in the peel of red dragon fruit (Hylocereus polyrhizus) (Yong, YY et al., 2018). Red dragon fruit (Hylocereus polyrhizus) peel is a source of prebiotics in yogurt because of its insoluble fiber content. The fiber content in red dragon fruit (Hylocereus polyrhizus) peel also affects the fiber content in dragon fruit peel yogurt. The group of hypercholesterolemic Wistar rats that received dragon fruit peel yogurt showed an inhibition of weight gain, possibly due to the fiber content in the yogurt. Soluble fibre and prebiotics in red dragon fruit (Hylocereus polyrhizus) peel yogurt can contribute to the regulation of energy homeostasis. Weitkunat showed that energy as a result of the fermentation process of dietary fiber does not contribute to increasing body weight (Yang et al., 2020).

Bacillus lactis, Streptococcus thermophilus, Lactobacillus bulgaricus and Lactococcus lactis added to milk to produce fermented milk can stimulate metabolite products such as butyrate and reduce pathobionts that cause inflammation and impaired intestinal barrier function (Habib et al., 2019). The protein content in yogurt can control appetite by reducing the secretion of gastrointestinal hormones, thereby increasing satiety, suppressing short-term food intake and diet induced thermogenesis (Chungchunlam et al., 2015). The contribution of satiety regulation which is characterized by a decrease in food intake can be influenced by the whey protein contained in yogurt. Whey protein is known as fast protein because it can be quickly digested and increase the plasma concentration of amino acids rapidly at 40 to 2 hours after consumption and return to basal levels after 3–4 hours (Kung B, et al., 2018). The satiety-inducing effect of whey protein is triggered by a postprandial increase in circulating amino acids, plasma cholecystokinin and glucagon-like polypeptide-1. The tryptophan α-lactalbumin content in whey protein can increase satiety and decrease appetite and food intake (Simonson M, Boirie Y, Guillet C, 2020).

Table 2. indicated that the treatment group

Table 2. Mean levels of blood glucose, serum lipid profile and microbial activity parameters* in Wistar rats

Parameters tested	G1[a] (mean±SD)	G2[b] (mean±SD)	G3[c] (mean±SD)	G4[d] (mean±SD)	G5[e] (mean±SD)
Glucose					
pre	60.72±1.43	150.04±5.10	150.83±5.81	151.84±5.75	153.43±5.09
post	60.99±1.47	152.70±5.29	126.23±3.92	116.18±1.14	107.55±2.66
Δ	0.28±0.55	2.66±1.92	-24.60±5.77[a,b]	-35.66±5.01[a,b,c]	-45.88±6.06[a,b,c,d]
p	0.326	0.036*	0.001*	0.001*	0.001*
Total Cholesterol					
pre	84.93±2.17	190.41±4.33	187.81±2.80	188.08±3.20	188.08±3.83
post	86.04±1.98	193.15±4.61	127.78±1.55	111.54±4.18	103.89±3.09
Δ	1.11±0.89	2.74±2.25	-60.03±3.18 [a,b]	-76.54±6.61 [a,b,c]	-84.19±2.39 [a,b,c,d]
p[a]	0.050	0.053	0.001*	0.001*	0.001*
HDL					
pre	61.77±4.07	25.44±1.41	25.44±1.41	25.17±1.08	24.08±2.18
post	54.68±3.85	22.17±1.36	30.86±2.15	43.45±2.54	50.19±1.67
Δ	-7.09±1.36	-3.27±1.84	5.42±2.69[a,b]	18.28±2.52[a,b,c]	26.11±3.56[a,b,c,d]
p	0.001*	0.016*	0.011*	0.001*	0.001*
LDL					
pre	37.37±3.39	75.98±1.50	76.40±1.67	76.82±1.89	74.19±1.14
post	41.29±3.81	79.71±3.90	52.90±2.50	42.72±1.65	36.42±2.05
Δ	3.92±1.11	3.73±4.52	-23.50±3.56[a,b]		-37.77±1.93[a,b,c]
p	0.001*	0.139	0.001*	0.001*	0.001*
Triglyceride					
pre	75.48±4.86	128.62±2.69	128.20±2.48	126.79±2.04	126.08±3.15
post	77.25±3.85	132.71±4.72	114.80±3.23	103.10±2.25	90.69±3.74
Δ	1.78±1.48	4.08±2.24	-13.40±3.31[a,b]		
p	0.055	0.015*	0.001*	0.001*	0.001*
TPC					
post	4.07±0.30x10^2	4.34±0.57x10^2	4.33±0.71x10^2		4.41±0.64x10^2[a]

Sampling was done 14 days after induction of hypercholesterolemia and 28 days after start of treatment; G1: did not receive treatment; G2: Hypercholesterolemic; G3: Hypercholesterolemic, treated dragon fruit peel yogurt 1.8 ml/kg b.wt/day; G4: Hypercholesterolemic, treated dragon fruit peel yogurt 2.7 ml/kg b.wt/day; G5: Hypercholesterolemic, treated dragon fruit peel yogurt 3.6 ml/kg b.wt/day. Values represent the mean ± SD for observation mode on five rats in each group. Statistical analysis: p; paired t- test, significant difference ($p<0.05$); One-way analysis for variance (ANOVA), where significant, post hoc testing (least significant difference) was done for intergroup comparisons. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

[a]Statistically significant difference ($p<0.05$) when compared with G1 values

[b]Statistically significant difference ($p<0.05$) when compared with G2 values

[c]Statistically significant difference ($p<0.05$) when compared with G3 values

[d]Statistically significant difference ($p<0.05$) when compared with G4 values

that received 3.6 mL of red dragon fruit (Hylocereus polyrhizus) peel yogurt experienced the most reduction in fasting blood sugar levels compared to all other groups. The incidence of diabetes mellitus which is triggered through atherosclerosis can begin with hyperglycemia and hyperlipidemia as risk factors. Recent studies conducted by measuring blood glucose levels of hypercholesterolemic rats showed that hyperlipidemia was directly proportional to hyperglycemia. This study also showed that hypercholesterolemic rats also showed a higher increase in blood glucose levels than the control rats (normal). Administration of red dragon fruit (Hylocereus polyrhizus) peel yogurt can significantly reduce blood glucose levels in hypercholesterolemic rats. The results of this study are consistent with previous research which states that the red dragon fruit (Hylocereus polyrhizus) peel extract can significantly reduce serum glucose in hyperlipidemic rats (Marco et al., 2017).

Red dragon fruit (Hylocereus polyrhizus) peel yogurt has the potential to have a low glycemic index. Yogurt can release bioactive peptides and bacteriocins. β-casein-derived peptides released from yogurt can trigger goblet cells to secrete mucin either in vitro or in vivo. Simple carbohydrates can be broken down by the lactic acid bacteria found in yogurt to produce lactate, acetate, or propionate. The breakdown of carbohydrates, changes in metabolic output as well as the availability of important substrates that support the development of intestinal microbes can be affected by lactic acid bacteria (M. A. Fernandez et al., 2017). The potential for low glycemic index in yogurt can be possible because of the soluble fiber contained in dragon fruit peel yogurt. A high-fiber diet has a good effect on glycemic control (Saji et al., 2019).

Carbohydrate metabolism is related to fiber. Its physiological and metabolic effects depend on the type of fiber. The absorption of fluids and the formation of gel in the stomach is affected by water soluble fiber. The gel slows down gastric emptying and absorption of nutrients including glucose. This can cause a decrease in blood glucose levels (Ma□kowiak et al., 2016). The content of phenolic, flavonoids and anthocyanins in red dragon fruit (Hylocereus polyrhizus) peel affects the decrease in blood glucose levels. Phenolic is a phenol that is substituted in various tropical plants. The mechanism of hypoglycemia of flavonoid in red dragon fruit (Hylocereus polyrhizus) peel can occur through reducing oxidative stress, inhibiting GLUT 2 and increasing insulin retention. Hypoglycemia mechanism through reduction of oxidative stress occurs with the role of antioxidants contained in dragon fruit peel. Inhibition of GLUT 2 produced by intestinal mucosal can reduce glucose absorption and cAMP phosphodiesterase inhibitory activity so that it can retain insulin for a longer period of time. This process can increase the occurrence of insulin retention. Energy can be produced through the entry of glucose into cells (Hartajanie et al., 2020). Glucose will be stored in the liver and muscles as an energy source so that glucose levels can slowly decrease (Joshi & Prabhakar, 2020). Sucrose which is added to the production process of red dragon fruit (Hylocereus polyrhizus) peel yogurt will be broken down by lactic acid bacteria through a permease system to form glucose and fructose through the glycolysis pathway to produce lactic acid (Nurhadi B et al., 2023).

The anthocyanin content in red dragon fruit (Hylocereus polyrhizus) peel yogurt can help reduce blood glucose level in this study. Anthocyanins have an antidiabetic effect through the expression of FGF21 by increasing the action of insulin receptors. FGF21 is expressed in the liver and is involved in the regulation of glucose, fat and energy metabolism. The anthocyanin content in red dragon fruit (Hylocereus polyrhizus) peel yogurt as an exogenous ingredient of FGF21 can improve metabolic disorders, increase glucose tolerance, insulin sensitivity, regulating lipid oxidation, improving lipid profiles, attenuating hepatic steatosis and reducing body weights. Obesity, impaired glucose tolerance, insulin resistance, hypertriglyceridemia and liver injury can increase the circulation of FGF21. The activity of FGF21 is related to the receptor binding complex composed of cofactors called □-Klotho (Klb) and FGFRs and then elicits the intracellular signaling cascades. Disruption of the action of FGF21 is possible due to a decrease in the expression of receptors and the role of betacyanin in red dragon fruit peel yogurt (K. Y. Choo et al., 2019).

Table 2. showed that there are significant differences in the levels of TC, HDL-C, LDL-C and TG in all treatment groups before and after treatment ($p < 0.05$). Groups that received 3.6 mL of dragon fruit peel yogurt had the most decrease in TC, LDL-C, TG and increase in HDL-C levels, compared to the group that received 1.8 mL or 2.7 mL of dragon fruit peel yogurt. The decrease in levels of TC, LDL-C and TG of the treatment group that received 3.6 mL of dragon fruit peel yogurt (G5) were reaching 84.19±2.39 mg/dL; 37.77±1.9 mg/dL; and 35.39±5.97 mg/dL respectively, while the increase in HDL-C levels was 26.11±3.56 mg/dL. Werdiningsih stated that dra-

gon fruit peel at a dose of 1.44 grams can be used to improve lipid profiles in dyslipidemic male rats (Werdiningsih, 2017).

Recent studies suggest that a decrease in mean of serum TC is associated with a decrease in the LDL-C fraction. Anti-hypercholesterolemic therapy in CHD can be done by modifying risk factors, one of which is by controlling serum LDL-C level. Atherogenesis can also be prevented by increasing the mean of serum HDL-C level. HDL-C has a preventive function in the formation of plaque in blood vessels (Rodriguez, EB et al., 2016). HDL-C is also known as "good cholesterol" because HDL-C plays a role in the process of mobilizing TG and TC from plasma to liver where TG and TC will undergo a catabolic process and are subsequently eliminated in the form of bile acids. The fermentation process in dragon fruit peel yogurt not only creates a distinctive aroma and taste but can increase its antioxidant potential. Lactobacillus bulgaricus and Streptococcus thermophilus added to the mixture of red dragon fruit peel and milk also increase the nutritional value of the dragon fruit peel yogurt produced (Cahyati et al., 2021). Research showed that there was more betanin in fermented drinks made from red dragon fruit (Hylocereus polyrhizus) peel (1.42 %) when compared to red dragon fruit (Hylocereus polyrhizus) flesh (0.23-0.39 %) (Hua Q et al., 2018).

The increased expression of Insig1 and Insig2 was associated with an increase in TC levels. High insulin levels will induce overexpression of Insig1 and Insig2 in the liver, thereby triggering cholesterol synthesis. The content of flavonoids and betacyanin in dragon fruit peel yogurt can reduce insulin levels and consequently reduce the expression of Insig1, Insig2 and cholesterol levels. Administering purified pitaya peel betacyanin (PPBN) can reduce serum TG, TC, and LDL-C levels in HFD-fed mice based on the results of Song's research (Song, Chu, Xu, et al., 2016). Betacyanin can increase serum adiponectin levels while reducing levels of Fas and Fads2 expression. Adiponectin is secreted by adypocytes which function to regulate lipid and glucose metabolism. AdipoR2 acts as a receptor for adiponectin and mediates increased activity of AMPK and PPAR-□ ligand and even fatty acid oxidation and glucose uptake. Cpt1a, Cpt1b and Acox1 encode the rate-controlling enzymes of the fatty acid beta oxidation pathway. Fas and Fads2 are involved in fatty acid synthesis. The peroxisome proliferator activated receptor-gamma (PPAR□) is a Fas and Acox1 regulator which is also influenced by the betacyanin content in dragon fruit peel yogurt (Song, Chu, Xu, et al., 2016).

An increase in HDL levels in the group who consumed dragon fruit peel infusion at a dose of 800 mg/dL was greater compared to the group with a dose of 200 mg/dL and 400 mg/dL (Huang Y et al, 2021). The activity of Lecithin-cholesterol acyltransferase (LCAT) can increase due to the presence of flavonoids that act as antioxidants in red dragon fruit (Hylocereus polyrhizus) peel. This mechanism of increasing LCAT also affects the increase in HDL cholesterol level. LCAT is fuctioned as an enzyme that can convert free cholesterol into ester cholesterol so that it can bind to lipoprotein core particles and form HDL-C (Al-muzafar & Amin, 2017). The niacin content in dragon fruit peel yogurt plays a role in increasing HDL-C levels and lowering TG. Niacin can increase levels of HDL-apoAI particles and HDL-C biogenesis by inhibiting hepatocyte surface expression from □-chain ATP synthase and increasing hepatic expression of ABCA1. The vascular endothelial oxidative process and inflammatory pathophysiological events can be inhibited by niacin through an inhibitory mechanism of lipid-independent antiatherogenic properties. The physiological function of HDL-C can be improved by niacin through decreased MPO neutrophil release and macrophage inflammation. The inhibition process of hepatocyte triglyceride synthesis and increased intracellular degradation of post-translational apoB and apoB-containing VLDL and LDL-C particles can also be carried out by niacin (Zaid, RM et al., 2019).

The highest decrease in LDL-C levels was in the group that received 3.6 mL of dragon fruit peel yogurt. The decrease in LDL-C levels is directly proportional to the dose administered. The decrease in LDL-C levels is caused by the antioxidant and fiber content in the dragon fruit peel yogurt. Red dragon fruit (Hylocereus polyrhizus) peel contains flavonoid compounds, betacyanin, anthocyanin, pectin and total dietary fiber which are higher than the flesh. Polyphenolic components function as antioxidants that can reduce the risk of CHD and various inflammation. Betalains are water soluble polyphenolic pigments composed of betaxanthins and betacyanins. Betacyanins are composed of betalamic acid and acyclic amine group which are excellent electron donors which enables scavenge free radicals. Betacyanins are known as red-purple pigment in red dragon fruit (Hylocereus polyrhizus) peel while betaxanthins are yellow pigments (Rahayu et al., 2022). Red dragon fruit (Hylocereus polyrhizus) peel is a potential source of betalain (Arivalagan, M et al, 2021). Flavonoids are cofactors of cholesterol esterase coenzymes. The excretion of bile sap can be increased through the role of flavonoids by activating the enzyme cytochrome P-450. Cytochrome P-450 enzymes can bind to several components in bile, thereby reducing cholesterol in the blood. Flavonoids are also known to be able to capture and neutralize free radicals such as reactive oxygen species (ROS) or reactive nitrogen species (RNS). The OH group in phenol can repair damaged tissue or inhibit the inflammatory process. The mechanism of action of myeloperoxidase/LDL oxidation inhibition induced by nitrates through scavenging activity (deactivation) of lipoperoxyl radicals involves the role of betacyanin which can be found in red dragon fruit (Hylocereus polyrhizus) peel (Choo, K.Y et al., 2018). Anthocyanins in dragon fruit peel are suspected to have the ability to inhibit CETP activity so that there is no exchange between cholesterol and TG between HDL-C and LDL-C. Thus, HDL-3 does not change to HDL-2 so that HDL-C levels will increase while LDL-C levels will decrease. This condition will increase the clearance of excess free cholesterol to be carried to the liver which will then be degraded by the liver, and reduce LDL oxidation. The vitamin C content in dragon fruit peel is also thought to increase the cholesterol-7a hydroxylase enzyme which converts cholesterol into bile acids and bile salts in the liver which are then excreted into the intestine and excreted through faeces (Song, Chu, Yan, et al., 2016).

Catechin, epicatechin, routine, quercetin, myricetin and kempferol are flavonoid compounds that can be found in red dragon fruit peel. Catechin has the highest concentration in red dragon fruit (Hylocereus polyrhizus) peel and is thought to activate PPAR by increasing the level of mRNA expression genes from various adipogenic markers. Adinopectin, PPAR-□, FABP4 and LPL are adipogenic markers that can be activated by the role of catechins. PPAR-□ correlates with superoxide dismutase-1 (SOD1) expression in the aortic arch resulting in decreased LDL oxidation. M1 macrophage expression from PPAR-□ decreased when LDL was oxidized. PPAR-□ can also inhibit SREPB which is a transcription factor that functions to regulate the gene expression in cholesterol, fatty acids and triglyceride synthesis.

Red dragon fruit (Hylocereus polyrhizus) peel contains 69.3 % of total fiber with 14.82 % of soluble fiber and 56.50% of insoluble fiber (Angga et al., 2016). Fiber has a role in lowering LDL cholesterol levels by certain mechanisms. The mechanism in question is to reduce cholesterol absorption and bile acid reabsorption in the intestinal lumen. The excretion of large amounts of bile acids causes a decrease in the circulation of enterohepatic bile acids followed by an increase in the conversion of cholesterol to bile acids in the liver and an increase in the circulation of cholesterol in the blood to the liver. Expression of the gut-derived proglucagon gene and secretion of proglucagon-derived peptides including glucagon-like pepride 1 (GLP-1) and peptide YY (PYY) will increase when soluble fiber is fermented in the large intestine. This hormone plays an important role in inducing satiety. The process of inducing satiety is carried out by reducing the rate of gastric emptying, triggering glucose uptake from the blood and storing glucose in peripheral tissues and inhibiting glucagon secretion. The secretion of glucagon can trigger lipolysis and beta-oxidation which can increase fatty acids and Acetyl-CoA, which can lead to an increase in cholesterol (Machate DJ et al., 2020).

The mechanism of decreasing triglyceride levels in dyslipidemic rats after intervention can be done through the antioxidant content in dragon fruit peel yogurt. High plasma TG levels are associated with increased deposits of atherogenic LDL-C and increased mass transfer of cholesterol esters derived from lipoproteins containing apolipoprotein B (VLDL-C and LDL-C). TG play a role in cholesterol esterification as well as the process of forming HDL-C in blood plasma. TG catabolism is influenced by the increased stimulation of lipolytic activity of plasma lipoprotein lipases. Changes in serum lipid peroxide levels and antioxidant status in subjects with high cholesterol and LDL-C and low HDL-C levels can increase the susceptibility of LDL-C to oxidation that occurs in the circulation (Fosbøl & Torp-pedersen, 2019). One of the active flavonoid compounds in red dragon fruit peel is catechins. Catechin consists of epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epicatechin (EC) (Morais et al., 2019).

The active compound of catechin polyphenol at the gene level has an influence in the activation process of peroxisome proliferator-activated receptor-□lpha (PPAR-□). PPAR-□ activation by active compounds will stimulate the oxidation of free fatty acids in the liver, thereby reducing the synthesis of triglyceride-rich lipoproteins and lowering plasma TG concentrations and inhibiting the synthesis of ApoC-III. ApoC-III delays the breakdown of triglyceride-rich lipoproteins so that the process of inhibition of the PPAR-□ activator compound occurs. PPAR-□ activator compound will reduce the concentration of plasma triglycerides (Cassidy & Minihane, 2017). Flavonoids can play a role in improving dyslipidemia by increasing PPAR-□. Research conducted on rats showed that the mechanism for increasing PPAR-□ occurred through decreased expression of sterol regulatory element-binding protein 1c (SREBP-1c) in rat liver. This decreased SREBP-1c expression led to a decrease in triglyceride synthesis resulting in denovo formation of free fatty acids and an increase in acetyl-CoA carboxylase (ACC) activity in rat hepatocytes.

The flavonoids contained in the infusion of red dragon fruit peel (Hylocereus polyrhizus) can reduce TG levels in male dyslipidemic rats by 25.3 % (Analianasari& Apriyani, 2018). Anthocyanin can be found in red dragon fruit peel. Anthocyanins are a class of flavonoid compounds that are broadly divided into plant polyphenols. Polyphenols can capture free radicals and can prevent lipid peroxidation processes in the microsomes and liposomes so that they play a part in reducing the secretion of lipoproteins in the liver and intestines. Cholesterol esterification can be reduced through the role of polyphenols, thereby reducing the formation of cholesterol esters. Cholesterol esters are the main building blocks of chylomicrons and VLDL. The process of decreasing cholesterol ester formation can disrupt the formation of chylomicrons, VLDL, IDL, and LDL so that blood triglyceride levels also decrease. The mechanism of reducing cholesterol levels by anthocyanins in red dragon fruit peel is through the process of inhibiting cholesterol formation. Anthocyanins can activate AMP-Activated Protein Kinase (AMPK) (Mohammadi-Sartang, M et al, 2018). Energy homeostatic regulation to influence enzyme activity is also influenced by AMPK. AMPK can inhibit the action of the HMG-CoA reductase enzyme. HMG-CoA reductase is an enzyme involved in cholesterol synthesis. Increase in AMPK activity can inhibit cholesterol synthesis process and reduce TG levels. TC and TG synthesis processes can be inhibited through the activity of acetyl-coA carboxylase (ACC) 1 and ACC-2, which results in an increase in fatty acid oxidation and a decrease in fatty acid synthesis so that TG levels can be decreased (Mofid et al., 2019). Betacyanin pigment is a derivative of betalanine. Betalanine has been investigated for its benefits as a free antiradical and antioxidative compound (Mutiara Novatama et al., 2016). The content of betalanine in red dragon fruit (Hylocereus polyrhizus) peel is related to LDL-C in blood plasma. Betalain can work to inhibit the myeloperoxidase (MPO) enzyme and the nitrite enzyme which acts as the main mediator in lipid oxidation process (Patterson, E et al., 2016).

The mechanism of TG reduction by fiber (pectin) in dragon fruit peel yogurt is through delaying gastric emptying so that satiety lasts longer. The quantity of calories that enter becomes less due to the delay in gastric emptying. This results in reduced insulin secretion. Insulin secretion is in accordance with the action of HMG-CoA reductase. Decreased insulin secretion will be followed by inhibition of the action of the HMG-CoA reductase enzyme so that cholesterol and triglyceride synthesis decreases (Huang Y et al, 2021). Short chain fatty acid (SCFA) such as acetate, propionate and butyrate are produced by fermentation of dietary fiber in the intestine. The process of inhibition action of the HMG-CoA reductase enzyme starts from the entry of propionate into the liver. This process results in a decrease in cholesterol and triglyceride synthesis (Analianasari & Apriyani, 2018). The consumed fiber will be fermented by anaerobic bacteria partially or completely in the large intestine. The final fermentation product increases SCFA content. High levels of SCFA in the colon can trigger the production of Glucagon-Like Peptide n-1 (GLP-1) and Peptide YY (PYY). GLP and PYY are anorexigenic peptides secreted by enterocyte cells. The increased secretion of GLP and PYY will be accompanied by an inhibition process of the mobilization of free fatty acids from adipose tissue so that the production of VLDL in the liver decreases. This process can control TC and TG levels to remain in a normal position (Makki K et al., 2018).

The safety of dragon fruit peel yogurt products can be evaluated by the number of microorganisms. The number of microbes will decrease with increasing temperature and time during the processing. Pasteurization process helps the preservation of dragon fruit peel yogurt product for a certain period of time. Colon metabolism contributes to the overall metabolic process (Murota et al., 2018). Microbial metabolism can be affected by the flavonoid content in dragon fruit peel yogurt. Flavonoids can change colonic bioconversion and even trigger flavonoid-microbiota interactions. These interactions can increase the production of biological activity and bioavailability of SCFAs, bile acid metabolism, inflammatory status and is associated with systemic intestinal and hepatic functions (Lin X. et al., 2021). SCFA production plays a role in colonic health, dietary energy extraction and weight regulation (Cassidy & Minihane, 2017). The limitation of this study was not examine the spesific type of lactic acid bacteria so that it can not be known which type of bacteria most affects the gut microbiota.

CONCLUSION

Red dragon fruit (Hylocereus polyrhizus) peel yogurt is effective for improving blood glucose levels (45.88±6.06 mg/dL) and lipid profiles in hypercholesterolemic wistar rats. The effective dose to improve blood glucose levels, TC, LDL-C, TG and increase HDL-C levels of hypercholesterolemic rats is to administer red dragon fruit peel yogurt as much as 3.6 ml/kg bwt/day. Future research is expected to explore pro-inflammatory parameters such as IL-6 or TNF-□ so as to determine lipid peroxidation due to the cellular level.

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