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Effectiveness of synbiotic red dragon fruit yogurt on glucose and oxidative stress in metabolic syndrome rats

Efektivitas yogurt sinbiotik buah naga merah pada glukosa dan stress oksidatif tikus sindrom metabolik

Ninik Rustanti[1*], Nyoman Putri Ari Amelinda[2], Kharisma Dwi Febriandina[3], Martha Ardiaria[4], Ayu Rahadiyanti[5], Mursid Tri Susilo[6], Adriyan Pramono[7]

[1] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: ninik.rustanti@fk.undip.ac.id
[2] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: putriariamelinda@gmail.com
[3] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: kharismadf62@gmail.com
[4] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: ardiaria@yahoo.com
[5] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: ayurahadiyanti@fk.undip.ac.id
[6] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: mursid@fk.undip.ac.id
[7] Department of Nutrition Science, Faculty of Medicine, Diponegoro University. E-mail: adriyanpramono@fk.undip.ac.id

***Correspondence Author:**
Department of Nutrition Science, Faculty of Medicine, Diponegoro University. Jl. Prof. Mr. Sunario, Tembalang, Semarang 50275, Indonesia.
E-mail: ninik.rustanti@fk.undip.ac.id

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Abstract

Metabolic syndrome is still a global health problem, especially in Indonesia. Oxidative stress is related to metabolic syndrome because it is triggered by hyperglycemia. Synbiotic yogurt containing the whole red dragon fruit has antioxidant and synbiotic potential. This study aimed to determine the effect of synbiotic yogurt with whole red dragon fruit on fasting blood glucose (FBG) and malondialdehyde (MDA) levels in rats with metabolic syndrome. The design of this study was true-experimental, with a pre-post test and randomized control group design. A total of 24 male Sprague Dawley rats were divided into four groups (K-, K+, P1, P2). Groups K+, P1, and P2 were fed a high-fat, high-fructose diet (HFHFD) for 2 weeks. Groups P1 and P2 were administered synbiotic yogurt intervention of 0,009 mL/gBB/day and 0,018 mL/gBB/day, respectively, for 4 weeks. GOD-PAP method for FBG analysis and TBARS method for MDA analysis. Data were analyzed using the paired t-test and One-Way ANOVA test. The P1 and P2 groups experienced a significant decrease in FBG levels by 63,45% and 76,07%, respectively ($p<0,001$), and a significant decrease in MDA by 26,1% and 37,2%, respectively ($p<0,001$). In conclusion, the administration of synbiotic yogurt at 0,018 mL/gBB/day (200 mL/day for humans) for four weeks was effective in reducing FBG and MDA levels.

Keywords: Antidiabetes, red dragon fruit, probiotics, metabolic syndrome, yogurt

Abstrak

Sindrom metabolik masih menjadi masalah kesehatan global terutama di Indonesia. Stres oksidatif berkaitan dengan metabolik sindrom karena stres oksidatif dipicu oleh hiperglikemia. Yogurt sinbiotik dengan naga merah utuh memiliki potensi antioksidan dan sinbiotik. Tujuan penelitian untuk mengetahui pengaruh yogurt sinbiotik dengan buah naga merah utuh terhadap kadar gula darah puasa (GDP) dan malondialdehid (MDA) tikus sindrom metabolik. Desain penelitian ini adalah t*rue-experimental* dengan *pre-post test with randomized control group design*. Sebanyak 24 ekor tikus Sprague Dawley jantan dibagi 4 kelompok (K-, K+, P1, P2). Kelompok K+, P1, dan P2 diberi *high-fat high-fructose diet* (HFHFD) selama 2 minggu. Kelompok P1 dan P2 diberikan intervensi yogurt sinbiotik masing-masing 0,009 mL/gBB/hari dan 0,018 mL/gBB/hari selama 4 minggu. Metode GOD-PAP untuk analisis glukosa darah puasa dan metode TBARS untuk analisis MDA. Data dianalisis dengan uji *paired t-test* dan uji *One-Way* ANOVA. Kelompok P1 dan P2 mengalami penurunan kadar GDP secara signifikan masing-masing sebesar 63,45% dan 76,07% ($p<0,001$) serta penurunan MDA secara signifikan sebesar 26,1% dan 37,2% ($p<0,001$). Kesimpulan, pemberian yogurt sinbiotik kulit dan daging buah naga merah 0,018 mL/gBB/hari (200 mL/hari untuk manusia) selama 4 minggu efektif dalam menurunkan kadar GDP dan MDA.

Kata Kunci: Antidiabetes, buah naga merah, probiotik, sindrom metabolic, yogurt

Introduction

Metabolic syndrome (MS) is a global health problem, especially in Indonesia. Globally, over 20% of adults are thought to have metabolic syndrome, which presents a significant health, social, and financial burden (Mahmoud & Sulaiman, 2022) In Indonesia, 39% of adults have metabolic syndrome (28% of men and 46% of women). People who have metabolic syndrome are more likely to have cardiovascular morbidity and death because they are at a higher risk of type 2 diabetes, heart disease, and stroke (Sigit et al., 2020).

Oxidative stress is associated with metabolic syndromes. Oxidative stress can be triggered by obesity, hyperglycemia, and hyperlipidemia (Rahmawati, 2014; Zulfahmidah et al., 2021). A condition known as Hyperglycemia occurs when blood glucose levels are higher than usual. Chronic hyperglycemia has been demonstrated to cause β-cells to undergo pro-apoptotic effects by increasing oxidative stress and reactive oxygen species generation (Unuofin & Lebelo, 2020). Malondialdehyde (MDA) is a marker of oxidative stress and an indicator of oxidative damage to cells and tissues. MDA is a toxic aldehyde product of lipid peroxidation (Wu et al. 2019). As the number of metabolic syndrome components increases, MDA levels increase, while total antioxidant capacity (TAC) levels decrease (Abbasian et al., 2018).

Antioxidant defence can control the state of oxidative stress by transferring hydrogen and breaking the chain reaction (Francisqueti et al., 2017). By inhibiting intestinal α-glucosidase and pancreatic α-amylase enzymes, these antioxidants also have antidiabetic effects(Ratimba et al., 2019). Antioxidants are also found in red dragon fruit. The skin of red dragon fruit contains flavonoids, anthocyanins, betasianins, and betanins of 193,8 mg QE/g; 19,21 mg/g; 35,12 mg/g; and 9,44 mg/g, respectively, while the flesh contains 177,4 mg QE/g; 15,16 mg/g; 30,15 mg/g; and 7,44 mg/g, respectively (Khoo et al., 2022; Saenjum et al., 2021). The inhibition concentration (IC50) value of red dragon fruit peel is 64,0 μg/mL, while the flesh has an IC50 of 76,41 μg/mL (Pratiwi et al., 2021; Pratiwi et al., 2019). Both IC50 values are strong antioxidants, because they are in the range of 50-100 μg/mL (Maulidha et al., 2015).

Synbiotic red dragon fruit yogurt was prepared by combining the skin and flesh of the red dragon fruit. Yogurt is a synbiotic because of the presence of probiotics from lactic acid bacteria and oligosaccharides, which are prebiotics, in the flesh and skin of red dragon fruit. The content of oligosaccharides such as raffinose, stakiose, and FOS in red dragon fruit flesh (324,57 μg/100 (Rohin et al., 2014). The oligosaccharide content in red dragon fruit has prebiotic properties because it can withstand acidic conditions in the human digestive tract and stimulate the growth of *Bifidobacterium* and *Lactobacillus* bacteria (Nurhayati et al., 2015).

Previous studies by Prasanti found that yogurt with the addition of skin juice and red dragon fruit pulp juice (1:9) had an antioxidant activity of 60,182%, total lactic acid bacteria (LAB) of $3{,}80 \times 10^7$ CFU/g, a taste and aroma that was liked, color that was very liked, and texture that was somewhat liked by panelists (Prasanti, 2023). The total LAB count met the minimum standard for yogurt quality requirements according to the SNI (1×10^7 CFU/g bacteria). Putriningtyas' research showed that administering red dragon fruit peel yogurt at a dose of 1,8 g/200 BW to rats for 28 days can reduce blood glucose levels by 24,60 ± 5,77 mg/dL in hypercholesterolemic rats (Putriningtyas et al., 2021). Previous studies have found that administering synbiotic drinks from bengkuang juice and kefir grains for four weeks can reduce hepatic tissue MDA levels in hyperlipidemia model rats (Prabowo, 2020).

Therefore, whole-red dragon fruit yogurt has antioxidant potential, synbiotics, and favorable product acceptability. The ability of the whole red dragon fruit to reduce blood glucose levels in humans and experimental animals has been extensively studied. However, there has been no research on the effect of the administration of synbiotic yogurt with whole red dragon on malondialdehyde and blood glucose levels. in rats has not been reported previously. This is the first study to combine probiotic yogurt and red dragon fruit in rats with metabolic syndrome. This study aimed to determine the effects of synbiotic yogurt containing whole red dragon fruit on fasting blood glucose (FBG) and malondialdehyde (MDA) levels in rats with metabolic syndrome.

Methods

This study used a randomized control group design and a true experimental pre-test. The preparation of whole red dragon fruit yogurt was carried out at the ITP Laboratory and Microbiology Laboratory of the Department of Nutrition, Diponegoro University, while rat treatment and plasma MDA analysis were carried out at the PSPG Laboratory of Gadjah Mada University, Yogyakarta, from August to October 2023. Sprague Dawley rats were used as research subjects. Sprague Dawley rats are frequently utilized as models for metabolic syndrome research because of their vulnerability to diet-induced obesity and related metabolic disorders. The inclusion criteria were male Sprague-Dawley rats, body weight 150-200 grams, normal activity, age 8-12 weeks, and healthy. Patients with anatomical abnormalities were excluded from the study. The dropout criteria were illness, such as persistent diarrhea during the study, dead rats, refusal to eat, and weakness.

Based on the WHO criteria, each group had at least five rats, and one tail was added to each group to avoid dropping out, resulting in a total of 24 rats. These consisted of 6 healthy rats serving as negative controls (K-) and 18 rats conditioned for metabolic syndrome that were administered high-fat high-fructose diet (HFHFD) for 2 weeks. Then, rats with metabolic syndrome were randomly divided into positive controls (K+), treatment 1 (P1), and treatment 2 (P2) to ensure consistency and reliability of the experimental conditions.

A total of 24 rats were acclimatized for seven days. The rats were placed in individual cages with 70% RH, 12-hour lighting, and a temperature of 20-25^{o} C. Comfeed AD II as standard feed as much as 20 grams/200 grams of rat BW/day and drinking water was provided ad libitum until the end of the study (Octavia et al., 2017; Rahmawati et al., 2017). The composition of 100 g of comfeed AD II consisted of 12% water, 51% carbohydrates, 3-7% crude fat, 15% crude protein, 6% crude fiber, 0,6-0,9% phosphorus, 7% ash, and 0,9-1,1% calcium (Yuliana & Ardiaria, 2016). After acclimatization, the rats were fed AD II and randomized into four groups. Group K- only received drinking water and standard feed ad libitum while groups K+, P1, and P2 were conditioned with metabolic syndrome for 2 weeks by being given HFHFD using a gastric sonde derived from homogenized pure fructose 1 mL/200 g of rat BW/day, quail egg yolk 1 mL/200 g of rat BW/day, and pork oil 2 mL/200 g of BW (Octavia et al., 2017; Rahmawati et al., 2017). After the rats were fasted for 8-10 hours, as much as 2 mL of blood was collected through the retroorbital plexus for plasma MDA analysis and metabolic syndrome parameters, such as serum triglycerides (TG), Fasting Blood Glucose (FBG), and High-Density Lipoprotein (HDL) levels. In addition to blood analysis, the nasoanal length of rats was measured to determine obesity status using the Lee index formula (Kosnayani et al., 2021):

$$\text{Indeks Lee} = \frac{\sqrt[3]{body\ weight(g)}}{naso{-}anal\ lenght(cm)} \text{ x } 1000$$

If the rats experienced three of the five metabolic risk factors, they had metabolic syndrome including Lee index >300, HDL levels <35 mg/dL, fasting blood glucose levels >109 mg/dL, and triglyceride levels >114 mg/dL (Kosnayani et al., 2021; Octavia et al., 2017; F. C. Rahmawati et al., 2017).

The next stage was the intervention of synbiotic yogurt with whole red dragon fruit using a gastric sonde for 4 weeks. Whole-red dragon fruit synbiotic yogurt was prepared according to the method described by Prasanti 2023). Homogenization of red dragon fruit skin and flesh synbiotic yogurt was performed before intervention in experimental animals using a homogenizer. The yogurt dose based on fermented milk recommendations for humans is 100 mL/day and 200 mL/day (Riyanto & Muwarni, 2015). The dose conversion results were 0,009 mL/g/day for group P1 and 0,018 mL/g/day for group P2, which were administered in the morning once a day. The K- and K+ groups were fed Comfeed AD II as standard feed at a concentration of 20 grams/200 grams of rat BW/day. Following an 8–10 hour fast, 2 mL of blood was extracted via the retroorbital plexus for post-test plasma MDA analysis using the TBARS technique. The Lee index was assessed after the examination.

The data obtained included body weight measured once per week, daily feed consumption starting during the conditioning period, and food consumption levels. The MDA plasma *pre-* and *post-tests* Statistical Package for the Social Sciences (SPSS) software was used for statistical analysis. The Shapiro–Wilk test was used to check for normality. The Wilcoxon test was used if the data were not normally distributed, and the paired t-test was used to compare the data before and after treatment. If the data were normally distributed and homogenous, One-Way ANOVA and Post Hoc LSD tests were used to assess differences in influence between groups. The Brown-Forsythe test and post hoc Games-Howell test were used if the data were normally distributed and inhomogeneous. If the data were not normally distributed, the Mann-Whitney U test was performed after the Kruskal–Wallis test. The Health Research Ethics Committee approved this study. This study was approved by the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University Semarang (number 96/EC-H/KEPK/FK-UNDIP/VIII/2023).

Result and Discussion

Metabolic Syndrome Conditioning

As shown in Table 1, the HFHFD group had Lee index, triglyceride levels, and FBG levels exceeding normal values, whereas HDL levels were below normal values, indicating that the HFHFD group had metabolic syndrome with obesity, hypertriglyceridemia, hyperglycemia, and low HDL levels.

Table 1. Metabolic syndrome conditioning

Group	n	Mean ±SD			
		Lee Index	HDL (mg/dL)	Triglycerides (mg/dL)	FBG (mg/dL)
K-	6	287,34 ± 2,24[b]	88,03 ± 1,55[a]	64,49 ± 1,53[b]	73,83 ± 1,78[b]
K+	6	326,32 ± 2,30[a]	24,28 ± 2,30[b]	132,86 ± 2,90[a]	143,68 ± 6,17[a]
P1	6	329,84 ± 6,31[a]	25,17 ± 1,26[b]	135,10 ± 2,25[a]	144,76 ± 4,72[a]
P2	6	328,70 ± 3,82[a]	24,50 ± 1,25[b]	133,81 ± 1,82[a]	142,66 ± 5,31[a]
p value		<0,001[x*]	<0,001[y*]	<0,001[y*]	<0,001[x*]

* significant, [x]Brown-Forsythe test, [y]One-Way ANOVA test, [(a,b)] =Different notations indicate significant differences in post hoc Games-Howell and LSD tests.

Giving HFHFD to groups K +, P1, and P2 for two weeks resulted in the group experiencing four metabolic syndrome criteria, including obesity, hyperglycemia, hypertriglyceridemia, and decreased HDL cholesterol levels, so that metabolic syndrome conditions were achieved. This is similar to previous studies showing that administering HFHFD to rats for two weeks can result in hyperglycemia, hypertriglyceridemia, and decreased HDL cholesterol levels (Octavia et al., 2017; Rahmawati et al., 2017). In addition, administering HFHFD can also cause obesity in rats after 4 weeks (Yusni & Yusuf, 2022).

HFHFD promotes obesity, hyperglycemia, hypertriglyceridemia, and decreased HDL levels. Long-term high-fat intake results in increased body weight and obesity, which occurs because it is not balanced by increased fat oxidation, so that approximately 96% of fat is stored in the body (Dewi & Kartini, 2017). In addition, excess fat intake can result in hyperglycemia due to decreased expression of glucose transporter-4 (GLUT-4), which disrupts glucose mobilization into the cell membrane will be disrupted (Salsabila et al., 2020).

Hypertriglyceridemia due to high-fat intake is caused by the production of free fatty acids and lipids. Hypertriglycerides due to high-fat intake are caused by increased free fatty acid production and lipogenesis, which results in the formation of triglycerides from the bond between free fatty acids and glycerol (Salsabila et al., 2020). Increased low-density lipoprotein (LDL) and cholesterol due to excess fat intake cause the breakdown of low-density HDL by kinetic lipase, which results in decreased HDL (Salsabila et al., 2020). Excess fructose intake can also promote overweight and obesity associated with impaired satiety signals in the brain (Fatmawati, 2019). In addition, excess fructose intake can result in the accumulation of cholesterol and triglycerides caused by the stimulating effect of lipogenesis, which reduces insulin sensitivity and results in glucose intolerance (Gunawan et al., 2021).

Lee Index

As shown in Table 2, there was a significant difference (p<0,05) in the Lee index between all groups of rats before and after the synbiotic yogurt with whole red dragon fruit intervention.

Conversely, the Lee index decreased in the P1 and P2 groups, and increased in the K + and K+ groups.

Following the synbiotic yogurt intervention, there was notable variation in the Lee index between the groups.

Table 2. Lee index before and after intervention

Group	n	Mean ± SD (gram)			% Changes	p value
		Before	After	Δ Change		
K-	6	287,34 ± 2,24[b]	288,76 ± 2,24[d]	1,42 ± 0,84[c]	0,49	0,000[v*]
K+	6	326,32 ± 2,30[a]	332,77 ± 3,20[a]	6,45 ± 1,52[b]	1,98	<0,001[v*]
P1	6	329,84 ± 6,31[a]	297,04 ± 1,67[b]	-32,80 ± 5,52[a]	-9,94	<0,001[v*]
P2	6	328,70 ± 3,82[a]	292,78 ± 1,20[c]	-35,91 ± 4,26[a]	-10,93	<0,001[v*]
p value		<0,001[x*]	<0,001[y*]	<0,001[z*]		

* Significant, [w] paired t-test, [x] Brown-Forsythe test, [y] One Way-ANOVA test, [z] Kruskal Wallis test, (a,b,c,d) Different notations indicate significant differences in post hoc Howell, LSD, and Mann-Whitney tests.

The K + and K+ groups experienced an increase in the Lee index, which is thought to be due to the influence of age (Risdayani & Makmun, 2021). Age-related changes in preadipocytes, including decreased replication, decreased adipogenesis, and increased proinflammatory cytokines, result from *cellular senescence*. Older mice tend to release more proinflammatory cytokines that can activate surrounding cells into a proinflammatory state and inhibit adipogenesis, contributing to age-related lipodystrophy and fat redistribution (Yu et al., 2019).

The P1 and P2 groups had a lower Lee index after the intervention and were significantly different from that of the K+ group, indicating that the administration of the Lee index after the intervention was significantly different from that of the K+ group. Both doses of synbiotic yogurt effectively reduced the Lee's index. Although the body weights of the P1 and P2 groups increased at the end of the intervention, the length of the rats also increased, resulting in a decrease in the Lee index. In addition, the decrease in the Lee index can be attributed to the administration of synbiotic yogurt, which is thought to have potential as an anti-obesity (Hadi et al., 2020; Hijová, 2022). This is similar to the findings of Khairani et al., who found that synbiotic yogurt administered for 8 weeks was able to reduce the Lee index (Khairani et al., 2022). SCFA result from the fermentation of prebiotics. By preventing fat accumulation in adipose tissue and increasing energy expenditure and satiety-related hormones, SCFA produced by prebiotic fermentation can prevent the development of obesity (Hadi et al., 2020). Furthermore, it is believed that the mechanism by which synbiotics prevent obesity involves the release of gut hormones including Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY), which are anorexigenic neurotransmitters that decrease appetite (Hijová, 2022).

Fasting Blood Glucose Levels

As shown in Table 3, there was a significant decrease in the average fasting blood glucose levels in groups P1 and P2 after administration of synbiotic yogurt with whole red dragon fruit ($p<0,05$). Group P2 (from 142,66 ± 5,31 mg/dL to 89,57 ± 3,22 mg/dL; Δ = 53,09 ± 8,11 mg/dL) had a greater decrease in mean fasting blood glucose levels compared to group P1 (from 144,76 ± 4,72 mg/dL to 106,90 ± 3,01 mg/dL; Δ = 37,87), ± 7,01 mg/dL). In the K- and K+ groups, which were only given standard feed without the provision of synbiotic yogurt with whole red dragon fruit during the intervention period, the mean fasting blood glucose levels increased (ΔK- = 1,41 ± 0,29 mg/dL and ΔK+ = 0,86 ± 0,26).

As shown in Table 3, there were differences between groups K- with K+, P1, and P2 at the time of pre-intervention (metabolic syndrome conditioning). There was no significant difference between groups K+, P1, and P2 based on the post-hoc Games-Howell test. Meanwhile, there was a significant difference in fasting blood glucose levels between groups K-, K+, P1, and P2 after the intervention with red dragon fruit skin and flesh synbiotic yogurt based on the post-hoc Games-Howell test.

Table 3. Fasting blood glucose levels before and after intervention

Group	n	Mean± SD (gram)			% changes	p value
		Before	After	Δ change		
K-	6	73,82 ± 1,77[b]	75,24 ± 2,03[d]	1,41 ± 0,29[c]	1,91	0,009[w*]
K+	6	143,68 ± 6,17[a]	144,54 ± 6,31[a]	0,86 ± 0,26	0,59	<0,001 [w*]
P1	6	144,76 ± 4,72[a]	106,90 ± 3,01[b]	-37,87 ± 7,01	-26,1	<0,001 [w*]
P2	6	142,66 ± 5,31[a]	89,57 ± 3,22[c]	-53,09 ± 8,11	-37,2	<0,001 [w*]
p value		<0,001[x*]	<0,001[y*]	<0,001[z*]		

* Significant, [w] paired t-test, [x] Brown-Forsythe test, [y] One Way-ANOVA test, [z] Kruskal Wallis test, [(a,b,c,d)] Different notations indicate significant differences in post hoc Howell, LSD, and Mann-Whitney tests.

Examination of the variations in fasting blood glucose levels revealed that the K-, K +, P1, and P2 groups had different fasting blood glucose levels. Fasting blood glucose levels decreased significantly in P1 (-37,87 ± 7,01 mg/dL) and P2 (- 53,09 ± 8,11 mg/dL). The results of this study are in accordance with research on the administration of 3,6 mL banana horn flour synbiotic yogurt for 14 days in metabolic syndrome rats can reduce fasting blood glucose levels by 46,83 ± 3,22 mg/dL (F. C. Rahmawati et al., 2017). According to another study, Sprague Dawley rats fed a high-fat diet saw a 37,4% drop in blood glucose levels after receiving 3,6 doses of beet tuber yogurt and cinnamon at a dose of 3,6 mL for 28 days.

Owing to the presence of probiotics, antioxidants, and fructooligosaccharides in the skin and flesh of dragon fruit, synbiotic yogurt containing these ingredients can lower blood glucose levels. Flavonoids, anthocyanins, and betasianins are among the antioxidants found in the skin and flesh of the red dragon fruit (Hylocereus polyrhizus). Flavonoids can restore the sensitivity of insulin receptors in cells exposed to free radicals and facilitate glucose transport into cells by increasing the cell membrane permeability to glucose. Other studies have reported that flavonoids can inhibit pancreatic β-cell damage and stimulate the release of insulin into the blood (Elvina & Adriaria, 2016; Putriningtyas et al., 2021).

Anthocyanins can reduce oxidative stress and Reactive Oxygen Species (ROS), thereby exerting a protective effect on pancreatic β-cells (Khoo et al., 2022). As an antioxidant, anthocyanins protect β-cells against oxidative stress-induced apoptosis and increase β-cell proliferation to restore pancreatic β-cell function. Anthocyanins protect β-cells from oxidative stress-induced apoptosis, decrease the levels of proinflammatory cytokines IL-1, IL-6, and TNF-α, and promote β-cell proliferation to restore β-cell function by secreting insulin (Al-Ishaq et al., 2019; Rajendiran et al., 2018; Unuofin & Lebelo, 2020). Anthocyanins also have antidiabetic effects via blocking the α-glucosidase and α-amylase enzymes anthocyanins also have antidiabetic effects via blocking the α-glucosidase and α-amylase enzymes (Oliveira et al., 2020). In diabetic rats, betasianin exerts a protective effect on pancreatic cells by lowering ROS levels (Putri et al., 2021). Betasianin also enhances adiponectin synthesis and insulin sensitivity (Solikhah et al., 2022).

Based on previous research, the total amount of LAB in synbiotic yogurt with whole red dragon fruit was 3,8 ± 2,4 × 10^7 CFU/mL, which met the probiotic drink standard of 10^7 CFU/mL. The study also showed that there was a difference in the total amount of LAB in synbiotic yogurt with red dragon fruit skin and flesh with yogurt without red dragon fruit (0.13 ± 0,577 × 10^7 CFU/mL). This is thought to be because of the potential of fructooligosaccharide compounds in red dragon fruit as prebiotics that can stimulate LAB growth (Prasanti, 2023). *Lactobacillus* and *Bifidobacterium*, two Gram-positive probiotic bacteria found in yogurt, help reduce the number of Gram-negative bacteria, which lowers LPS and inflammatory markers. They can also improve blood glucose profiles by promoting the production of glucagon-like peptide-1 (GLP-1) and insulinotropic polypeptides, which increase glucose absorption (Nuriannisa et al., 2019).

Research has shown that *Lactobacillus casei* and *Bifidobacterium bifidum* lowered fasting blood glucose levels in a 28-day intervention and helped in the management of metabolic syndromes. Probiotic bacteria increase insulin sensitivity by attenuating local inflammation. Administration of *Lactobacillus* *casei* and *Bifidobacterium bifidum* alone or in combination significantly decreased the level of lipid peroxidation in diabetic rats, suggesting that probiotics provide antioxidant activity and protect the pancreas from lipid peroxidation. (Sharma et al., 2016). Another study revealed that *Streptococcus thermophilus* bacterial strains have the ability to biosynthesize folic acid and *gamma aminobutyric* acid (GABA), which function in the process of cell regeneration and replication to restore β-cell damage that occurs due to oxidative stress (Nuriannisa et al., 2019).

In addition to probiotic bacteria, it is suspected that prebiotics in red dragon fruit skin and flesh synbiotic yogurt could reduce blood glucose levels. Prebiotics are thought to originate from the fructooligosaccharide content of the red dragon fruit flesh. Because fructooligosaccharides, which are prebiotics, cannot be broken down by tiny intestinal enzymes, colonic bacteria ferment them to produce SCFA in the form of propionic acid, which can decrease insulin resistance and block gluconeogenesis in the liver. Additionally, SCFA can enhance GLP-1 production, which can then connect to its particular receptors on pancreatic β-cells to promote the secretion of insulin (Le Bourgot et al., 2018).

Flavonoids have been found to beneficially alter intestinal metabolic responses in subjects with metabolic syndrome features through various pathways, including microbiota modulation and DNA methylation, increasing short-chain fatty acid (SCFA) production, especially butyrate, and potentially reducing intestinal inflammation (Maurer Sost et al., 2023).

Malondialdehyde (MDA) levels

As shown in Table 4, all groups had different MDA levels before and after the synbiotic yogurt with red dragon fruit skin and flesh intervention (p<0,05). Although the MDA levels decreased in the P1 and P2 groups, they increased in the K + and K+ groups. Furthermore, following the synbiotic yogurt intervention, there were notable variations in MDA levels across the four groups. *The Brown-Forsythe* test indicated significant differences (P <0,05) in the changes in MDA levels between the groups. The largest decrease in MDA level (76,07%) was observed in P2.

Table 4. Malondialdehyde levels before and after intervention

Group	n	Mean ± SD (nmol/mL)			% changes	p value
		Before	After	Δ Change		
K-	6	1,36 ± 0,18^{c}	1,53 ± 0,24^{d}	0,18 ± 0,07^{c}	13,02	0,002^{w*}
K+	6	10,43 ± 0,38^{b}	10,68 ± 0,57^{a}	0,25 ± 0,21^{c}	2,38	0,032^{w*}
P1	6	10,78 ± 0,48^{a,b}	3,94 ± 0,41^{b}	-6,84 ± 0,38^{b}	-63,45	<0,001^{w*}
P2	6	10,91 ± 0,41^{a}	2,61 ± 0,33^{c}	-8,30 ± 0,66^{a}	-76,07	<0,001^{w*}
p value		<0,001^{y*}	<0,001^{y*}	<0,001^{x*}		

*significant, ^{w} Paired t-test, ^{x}Brown-Forsythe test, ^{y}One-Way ANOVA test, $^{(a,b,c,d)}$= Different notations indicate significant differences in post-hoc LSD and Games-Howell tests.

The significant difference in MDA levels between the HFHFD group (K+, P1, and P2) and the group without HFHFD (K-) indicates that administering HFHFD for two weeks can increase MDA levels. A previous study found that superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities in the liver dramatically decreased after receiving HFHFD for four weeks, but MDA and nitric oxide (NO) levels increased. (Abdelmoneim et al., 2021). This indicates that HFHFD reduces the enzymatic antioxidant potential of the body, making it more difficult for the body to resist oxidative damage and free radical production. Increased lipogenesis due to a high-fructose diet may trigger ectopic lipid accumulation, mitochondrial oxidative stress, and decreased antioxidant defense against oxidative stress. The pathophysiology of cardiometabolic disease dysfunction is further driven by the increased formation of advanced glycation end products (AGEs) from fructose, which promotes the generation of reactive oxygen species (ROS) via NADPH oxidase and mediates inflammatory pathways (Bernardes et al., 2017).

Consuming excessive fat can promote β-oxidation of free fatty acids in the mitochondria, which can lead to excess electron flow via cytochrome c oxidase and a greater build-up of ROS. (Tan & Norhaizan, 2019). In addition, as the number of metabolic syndrome components increases, the level of total antioxidant capacity decreases, while MDA levels increase (Abbasian et al., 2018). There was a difference in MDA levels before the intervention between the K+ and P2 groups, but there was no difference in MDA levels between the P1 and K+ groups or the P1 and P2 groups. While there was a statistically significant difference in MDA levels between groups K+ and P2 prior to the intervention, the clinical difference of 0,48 nmol/mL cannot be considered significant.

The plasma MDA levels in all groups were significantly different before and after the intervention ($p<0,05$). The K + and K+ groups showed increased MDA levels, which was thought to be due to the influence of age. A previous study found that an increase in serum MDA levels occurred with age in experimental animals (Ahsani & Fidianingsih, 2018). Changes in the concentration of antioxidant enzymes can occur with age; therefore, the body cannot overcome the increase in free radicals (Ahsani & Fidianingsih, 2018). On the other hand, groups P1 and P2 experienced a decrease in MDA levels due to the administration of synbiotic yogurt with red dragon fruit skin and flesh.

Synbiotic yogurt whole red dragon fruit can lower plasma MDA levels by 63,45% when administered at a dose of 0,009 mL/gBB rat/day for four weeks, and by 76,07% when administered at a dose of 0,018 mL/gBB rat/day. The results of this study are similar to a study that found that the administration of synbiotic drinks for 4 weeks can reduce hepatic tissue MDA levels with the lowest average MDA levels in the highest dose group, namely 4,1 ± 0,09 nmoL/gram in rat models (Prabowo, 2020). Probiotic/synbiotic therapy can significantly increase blood total antioxidant capacity (TAC), reduce glutathione (GSH) and NO levels, and lower MDA levels in adults, according to a systematic review and meta-analysis (Pourrajab et al., 2021).

Following synbiotic yogurt intervention, MDA levels in the P1 and P2 groups reduced in accordance with the Lee index level. TAC level and abdominal obesity showed an inverse relationship, whereas MDA level and BMI showed a significant positive correlation. These findings suggested that obesity alters the cellular antioxidant system and increases the number of active free radicals. (Abbasian et al., 2018). Groups P1 and P2 experienced a decrease in the level of obesity, as seen from the Lee index, and became non-obese (Lee index <300) after the intervention, thus reducing the MDA levels. Furthermore, the administration of synbiotic yogurt containing the antioxidant skin and flesh of red dragon fruit resulted in a decrease in MDA levels, although the P1 and P2 groups' body weights increased at the conclusion of the intervention.

Prasanti found that yogurt with red dragon fruit skin and flesh juice (1:9) had an antioxidant activity of 60,182% (Prasanti, 2023). The antioxidant qualities of several ingredients found in red dragon fruit skin and flesh synbiotic yogurt, such as the antioxidant qualities of proteins (casein and whey), probiotics, prebiotics, and phytochemicals found in red dragon fruit, are assumed to be the cause of the improvement in rat MDA observed in this study. Arachidonic acid peroxidation linked to the Fe-binding capacity of phosphoserine residues—ten, five, and one in α-, β-, and κ-casein, respectively, —can be inhibited by all casein subunits. (Fardet & Rock, 2018). Whey proteins can form GSH as an intracellular antioxidant by converting the intracellular amino acid cysteine (Susanti & Hidayat, 2016). In addition, lactoferrin, as an antioxidant, can bind iron to prevent it from acting as a Haber-Weiss catalyst (Rodzik et al., 2020). The peptides released during hydrolysis can counteract free radicals, bind metal ions, and/or inhibit lipid peroxidation (Fardet & Rock, 2018).

Previous research by Prasanti (2023) showed that red dragon fruit skin and flesh juice yogurt (1:9) contained LAB of $3,80 \times 10^7$ CFU/g (Prasanti, 2023) and administration of the probiotic *Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, *Lactobacillus delbrueckii bulgaricus* LBY-27 for eight weeks showed that the levels of MDA, glutathione reductase (GSHR), and erythrocyte GPx were significantly improved when compared to placebo (Hajifaraji et al., 2018). Probiotics have the ability to bind Fe^{2+} and Cu^{2+} metal ions so that they can inhibit the formation of hydroxyl radicals (Feng & Wang, 2020; Nocianitri et al., 2016). According to a previous study by Lin and Yen, of the 19 strains investigated, S. thermophilus 821 had the best Fe2+-binding ability, and B. longum 15 708 had the highest Cu2+-binding ability. Furthermore, probiotics can control antioxidant enzymes (Feng & Wang, 2020).

Probiotics also have antioxidant properties that are related to signaling pathways

(Feng & Wang, 2020). In a mouse model of Alzheimer's disease, a combination of *Bifidobacteria, Lactobacili,* and *S. thermophilus* can lower oxidative stress, primarily through a marked upregulation of the expression and activity of silent information regulator 1 (SIRT1) (Bonfili et al., 2018). By activating AMP-activated protein kinase (AMPK) and AKT, probiotics that can create butyrate can stop the oxidative damage-related Non-alcoholic Fatty Liver Disease (NAFLD) from developing. AKT phosphorylation and nuclear factor erythroid 2-related factor 2 (Nrf2) activation in vitro can result from SIRT1 phosphorylation and nuclear translocation, induced by sodium butyrate-mediated AMPK activation.

Probiotics can also produce antioxidant molecules such as exopolysaccharides (EPS) and modulate gut flora (Feng & Wang, 2020) It is known that the fermented milk-derived *Lactobacillus delbrueckii sp. bulgaricus* SRFM-1 produces EPS, which possesses antioxidant qualities (Tang et al., 2017). The EPS fraction showed strong scavenging activity on superoxide radicals, hydroxyl radicals, DPPH radicals, and binding activity on iron ions. *Lactobacillus* and *Bifidobacterium* can produce propionic acid, lactic acid, and acetic acid, which can balance the intestinal flora by lowering the intestinal pH and inhibiting the proliferation of harmful bacteria, thereby suppressing oxidative stress (Wang et al., 2017). Administration of probiotic *Bifidobacterium infantis*, *Lactobacillus acidophilus*, and *Bacillus cereus* can increase the levels of these anaerobic bacteria and decrease aerobic bacteria (*Escherichia coli* and *Enterococcus*) in fecal samples of mice fed a high-sugar, high-fat diet, and can also improve intestinal endotoxemia (Xue et al., 2017). This study found that probiotics can improve intestinal flora disorders and increase occludin expression, thereby inhibiting bacteria or endotoxins from entering the blood and decreasing TLR4 expression in the liver, thereby reducing hepatic and systemic inflammatory responses through LPS/TLR4 signaling.

In addition to probiotic bacteria, prebiotics are thought to increase MDA levels. Yogurt with the addition of more meat juice compared to skin juice (9:1) can produce higher total LAB (3,80x10^7 CFU/g) and is significantly different from the yogurt control group without the addition of red dragon fruit juice (0,13x10^7 CFU/g) (Prasanti, 2023). This is thought to be due to the prebiotic properties of oligosaccharide compounds in red dragon fruit, which can increase LAB growth (Prasanti, 2023). The content of oligosaccharides (raffinose, stachyose, and FOS) in the flesh of red dragon fruit (324,57 µg/100 g; 283,58 µg/100 g; 149,32 µg/100 g) was higher compared to the skin of red dragon fruit (32,59 µg/100 g; 30,23 µg/100 g; 29,22 µg/100 g) (Rohin et al., 2014). SCFAs such as butyrate, butyrate, and FOS were higher than those of red dragon fruit skin (32,59 µg/100 g; 30,23 µg/100 g; 29,22 µg/100 g, respectively) SCFAs, such as butyrate, propionate, and acetate, are the main end products of bacterial fermentation (Nisa et al., 2021). SCFAs, such as butyrate can stimulate the formation of NADPH to produce GSH, induce apoptosis, and reduce the risk of death (Asemi et al., 2014). Additionally, by transcriptionally activating nuclear factor erythroid 2 related factor 2 (Nrf2) via P300, SCFAs such as butyrate can reduce diabetes-induced aortic endothelial dysfunction (Wu et al., 2018).

Red dragon fruit, both skin and flesh, contains flavonoids, anthocyanins, betacyanin's, and betanin, which act as antioxidants (Khoo et al., 2022; Saenjum et al., 2021). This study did not directly test the phytochemical content of synbiotic yogurt as a whole. However, flavonoids as antioxidants can directly overcome free radicals through hydrogen ion donors while indirectly increasing the expression of endogenous antioxidant genes through Nrf2 activation (Septiana & Ardiaria, 2016). Anthocyanins act as antioxidants by single electron transfer and hydrogen atom transfer to convert free radicals into more stable products (Garcia & Blesso, 2021), binding to transition metal ions to form stable anthocyanin-metal complexes, preventing the formation of highly toxic and reactive hydroxyl reactions from being formed (Rusip et al., 2022), and can also activating Nrf2 and antioxidant enzymes, and increasing their enzymatic activity (Salehi et al., 2020). Betacyanin can increase the expression of Nrf2, which can increase the expression of antioxidative factors, such as heme oxygenase 1 (HO-1), GCLM, and SOD, thereby suppressing the formation of ROS (Chenxu et al., 2021). The antioxidant ability of Betanin is an electron and hydrogen donor derived from cyclic amines and hydroxyl groups (Da Silva et al., 2019), and increases antioxidant capacity via the Nrf2-

mediated pathway (Mousavi et al., 2022). Although animal models are essential for elucidating biological systems, their applicability in humans is limited. The applicability of the results to human populations may be influenced by physiological differences between species. Future studies should involve clinical trials to validate our findings in humans.

Conclusion

The administration of synbiotic yogurt with whole red dragon fruit doses of 0.018 mL/gBB rat/day (200 ml/day for humans) for 4 weeks effectively reduced fasting blood glucose and plasma MDA levels in Sprague Dawley rats with metabolic syndrome.

Therefore, it is possible to conduct trials on the effects of synbiotic yogurt with 200 mL/day of whole red dragon fruit for four weeks in humans. Thus, consumption of synbiotic yogurt with 200 mL of whole red dragon fruit per day for 4 weeks can help reduce fasting blood glucose levels and oxidative stress. It can be used as a functional food alternative for individuals with metabolic syndrome to improve metabolic health and reduce the risk of complications.

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