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Effectiveness Analysis of Antidiabetic Property from Dragon Fruit Peel Methanol Extract in Alloxan-Induced Diabetic Rats

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Abstract

Diabetes is a health burden in various countries, one of these countries, is also Indonesia. Dragon fruit peel is an alternative diabetes therapy that has been widely studied. Therefore, this study aimed to investigate an antidiabetic effect of dragon fruit peel methanol extract on alloxan-induced diabetic male Wistar rats. This experimental study used twenty-five male Wistar rats induced by alloxan injection. After 48 hours, all rats were grouped into five different groups, including control (0.5% SCMC), standard (Metformin), Dragon Fruit Peel Methanol Extract-1 (500 mg/kg BW), 2 (750 mg/kg BW), and 3 (1,000 mg/kg BW). These treatments were given for two weeks. After that, all rats were dissected to obtain the pancreas. The results showed that dragon fruit peel methanol extract significantly decreased blood glucose levels after the 7^{th} and 14^{th} days (P value <0.05). In addition, pancreatic histology showed a decrease in the extract dose followed by a smaller size of the pancreatic Langerhans islet. The lowest dose of the extract showed a similar size of pancreatic Langerhans islet to the control group with an atrophic pancreatic Langerhans islet. Therefore, it can be concluded that dragon fruit peel extract can significantly decrease blood glucose levels and improve the structure of pancreatic Langerhans islet at higher doses.

Keywords: Anti Diabete; Dragon Fruit Peel; Langerhans Islet; Pancreas.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both. Chronic hyperglycemia in diabetes is associated with long-term damage or dysfunction of several body organs, especially the eyes, kidneys, nerves, heart, and blood vessels. World Health Organization (WHO) has reported that diabetes mellitus cannot be briefly described. However, WHO generally defines diabetes mellitus as an accumulation of anatomical or biochemical dysfunction caused by some factors that lead to either absolute or relative insulin deficiency with or without insulin dysfunction. (Purnamasari, 2014)

Diabetes is a health burden in various countries, and one of these countries is Indonesia. It is due to the long-term impact of diabetes mellitus, including blindness, heart disease, and kidney failure. The International Diabetes Federation (IDF) estimates that at least 463 million people aged 20-79 years old worldwide had diabetes in 2019, or equivalent to a prevalence rate of 9.3% of the total population of the same age. Based on gender, IDF estimates that the prevalence of diabetes in 2019 will be 8% in women and 9.65% in men. The prevalence of diabetes is estimated to increase as the population ages 19.9% (111.2 million people) aged 65-79 years. This rate is estimated to grow annually to 578 million in 2020 and 700 million in 2045 (Internation Diabetes Federation, 2019).

Recently, herbal medicine is a medicine that is quite popular and is in relatively high demand on the market. It can be seen from the increasing number of herb industry. The Food and Drug Monitoring Agency (*Balai Pengawasan Obat dan Makanan*/ BPOM) reports that the annual growth rate in the herbal medicine industry ranges from 25% to 40%. Pranomo (2022) reported that 810 active factories were producing traditional Indonesian medicines; 87 factories were IOAT (Traditional Medicine Industries), and the remaining 723 were Small Herbal Medicine Industries). In a prior report, it was reported that 872 companies work in the herbal industry. Ironically, around 462 of these companies were foreign companies. Hence, it indicates that the utility of herbal medicines in society, especially in Indonesia, is very high because the herbal medicine industry annually increases (Elfahmi et al., 2014).

According to the information above, the herb industry quietly developed in Indonesia and has become a potential alternative medicine, especially for diabetes mellitus, and Indonesia, as part of Southeast Asia countries, has a high prevalence and incidence rate of diabetes mellitus. A natural product widely studied is

dragon fruit peel. Several studies have reported various health benefits of dragon fruit peel. Mahargyani (2019) reported that the n-hexane fraction of dragon fruit peel extract had α-glucosidase enzyme inhibitory activity with an IC_{50} value of 194.11 ppm, while acarbose was 5.6 ppm. Putri et al. (2020) also reported that red dragon fruit reduced plasma HOMA-IR and MDA plasm, which had a similar effect to metformin. Another study that was performed by Panjaitan and Novitasari (2021) also reported that red dragon fruit peel ethanol extract had antidiabetic activity at a dose of 74.88 mg/ 200 grams BW in streptozotocin-induced diabetic rats and this effect was similar to glibenclamide at a dose of 0.09 mg/ 200 grams BW (Mahargyani, 2019; Panjaitan & Novitasari, 2021; Putri et al., 2021).

Even though many studies have been performed to explore the antidiabetic effects of dragon fruit peel, none of these studies explore the antidiabetic effect of dragon fruit peel extract and its effect on pancreatic tissue. Hence, this study aimed to investigate an antidiabetic effect of dragon fruit peel methanol extract on alloxan-induced diabetic male Wistar rats.

MATERIALS AND METHODS

Study Design

This experimental study was performed between September 2022 to December 2022 in the Pharmacology Laboratory, Universitas Prima Indonesia. This study protocol has been approved by the Health Research Ethics Committee Universitas Prima Indonesia with letter no. 019/KEPK/UNPRI/XII/2022.

Materials

This study used some materials, including dragon fruit peel, 98% methanol solution, distilled water, SCMC (Sodium Carboxyl methylcellulose), metformin tablet, rat food pellets and bedding, HCl, magnesium powder, amyl alcohol, Mayer's reagent, Bouchardat's reagent, Dragendorff's reagent, iron (III) reagent chloride, sulfuric acid, 95% ethanol, lead (II) acetate, isopropanol, chloroform, Molisch reagent, Lieberman-Bourchard reagent, acetic acid, and ketamine.

Extraction Process

This study used dragon fruit peel that initially dried and meshed into simplicial powder. Dragon fruit peel simplicial powder was soaked into 98% methanol solution with a ratio of 1:3, also known as the maceration process. Then, it was regularly stirred for three days. Afterward, it was filtered, and the residue was re-macerated as before two times. All filtrates were then collected to evaporate by rotary evaporator at a temperature of 40-50^{o}C until formed concentrated extract. After that, the extract yield was a ratio of the extract and the simplicial powder mass, which was expressed as a percentage (Mutia, 2019) (Chiuman et al., 2021; Suhartomi et al., 2020).

Phytochemical Screening

This study underwent a phytochemical screening based on the standard manual for phytochemical screening from the Pharmacology Laboratory of Universitas Prima Indonesia, including phenolic, flavonoid, alkaloid, terpenoid/ steroid, tannin, and saponin (Depari et al., 2021; Widowati et al., 2017).

Oral Suspension Formulation

This study used 0.5% SCMC as a vehiculum for both metformin and dragon fruit peel extract to administer it via the oral route by oral gavage feeding tubes. This vehiculum was formulated by dissolving 500 mg sodium carboxymethylcellulose powder into a hundred milliliters of warm distilled water. After that, amount of 400 mg dragon fruit peels methanol extract and 100 mg metformin were suspended into 10 ml 0.5% SCMC to form dragon fruit peels methanol extract and metformin oral suspension, respectively (Chiuman, 2019; Kanon et al., 2012; Mutia & Chiuman, 2019).

Alloxan Induction

Alloxan induction was performed by subcutaneous alloxan induction. This study used a 5% alloxan monohydrate solution with a dose of 3 ml/ kg BW (150 mg/ kg BW). Evaluation of diabetic condition was performed after 48 hours of subcutaneous alloxan injection, and diabetic condition was defined as blood glucose level higher than 200 mg/ dl (11.1 mmol/ L) (Ighodaro et al., 2017a; Nair & Jacob, 2016; Njagi E N Mwaniki & Njagi J Murugi, 2015).

Antidiabetic Assay

The antidiabetic assay was performed on twenty-five diabetic rats and grouped into five treatment groups. These groups were standard (metformin), control (0.5% SCMC), dragon fruit peel-1 (500 mg/ kg BW), 2 (750 mg/ kg BW), and 3 (1,000 mg/ kg BW), that received a milliliter of 0.5% SCMC, a milliliter of metformin oral suspension, 5, 7.5, and 10 ml/ kg BW of dragon fruit peel extract oral suspension, respectively. These treatments were performed for two weeks. All rats were free to access rat food pellets and beverages.

Blood Glucose Measurement

This study measured fasting blood glucose level, which was measured after 10-12 hours of fasting periods. Blood glucose level was obtained from the tail vein, and fasting blood glucose was measured before induction, 48 hours after induction, and two weeks after treatment (Zubaidah et al., 2019).

Pancreas Tissue Study

Pancreas tissue was dissected and preserved in a 10% formalin buffer solution. Then, all histology slides were

sliced with a 4-6 mm thickness, stained with hematoxylin and eosin, and observed under a microscope. Pancreas tissue processing and staining were performed based on the procedure in the anatomical pathology laboratory, Faculty of Medicine, Universitas Sumatera Utara.

Data Analysis

Blood glucose level and Initial body weight were analyzed by One-Way ANOVA if distribution data was normal, followed by Post Hoc Test Tukey HSD. Meanwhile, if data distribution was not normal, all data were analyzed by Kruskal-Wallis, followed by Mann-Whitney. On the other hand, the physical characteristics and phytochemical compounds of dragon fruit peel extract and pancreas tissue histology study were narratively described.

RESULTS AND DISCUSSION

This study used dragon fruit peel methanol extract that was obtained from a traditional market in Medan City. This study used 2,000 grams of dragon fruit peel as a fresh simplicial. After that, this fresh simplicial was dried and meshed into 1,896.9 grams of simplicial powder. This simplicial powder was macerated by 7,500 ml of methanol solution to obtain 79.97 grams of concentrated dragon fruit peel methanol extract. Based on these values, dragon fruit peel methanol extract yields 4.22%.

The obtained dragon fruit peel extract underwent phytochemical screening, revealing phytochemicals including phenol, flavonoid, alkaloid, and tannin. After that, this dragon fruit peel extract was evaluated for antidiabetic activity by an alloxan-induced diabetic rat model. All acclimatized rats were initially weighed; this initial body weight in grams was described in Table 1.

Table 1. Initial Body Weight of All Rats.

Group	Initial Body Weight, gram		P-Value
	Mean	SD	
Control	165.00	6.96	0.966
Standard	165.00	6.96	
Dragon Fruit Peel Extract-1	163.60	5.68	
Dragon Fruit Peel Extract-2	163.20	5.63	
Dragon Fruit Peel Extract-3	162.80	5.45	

Table 1 showed that there was no significant difference in the initial body weight of all rats; it can be seen from the P-value > 0.05 (P-value = 0.966). Thus, it can be concluded that the initial body weight of all rats used in this study was homogenous, a range of 162.80-165.00 grams. After that, these rats were diabetic-induced by alloxan injection, and then these rats were grouped to be treated based on the treatment groups, and a comparison of blood glucose levels in all rats was described in Table 2.

Table 2. Comparison of Blood Glucose Levels in All Treatment Groups.

Group	Blood Glucose Level (mg/dL), Mean ± SD			
	Before Induction	After Induction	7th day	14th day
Control	95.60 ± 7.30	390.00 ± 108.12	462.40 ± 88.13a	440.40 ± 100.98a
Standard	92.20 ± 3.96	432.00 ± 138.19	152.00 ± 18.30b	133.20 ± 9.09b
Dragon Fruit Peel Extract-1	89.40 ± 8.08	391.20 ± 102.05	327.60 ± 38.93c	203.80 ± 16.12b
Dragon Fruit Peel Extract-2	99.40 ± 3.65	471.40 ± 101.70	284.20 ± 86.17c	181.00 ± 19.71b
Dragon Fruit Peel Extract-3	93.00 ± 6.63	438.80 ± 132.50	238.20 ± 84.74bc	137.00 ± 24.75b
P-Value	**0.157**	**0.785**	**< 0.05**	**< 0.05**

P-value was obtained from the One-Way ANOVA Test; Different superscripts in the same column indicate significant differences based on the Tukey HSD Post Hoc Test.

Table 2 showed that there was no significant difference in the blood glucose levels of rats both before induction and after induction; it can be seen from the P-value > 0.05 in the blood glucose level data before induction (P-value = 0.157) and after induction (P-value= 0.785). It can be concluded that blood glucose levels, either before or after induction, were homogenous. Furthermore, blood glucose levels showed a significant change on the 7th and 14 days; it can be seen from the P-value < 0.05. In the first week of administering, the dragon fruit peel methanol extract showed a significant reduction in blood glucose levels compared to the control group; increasing the dose of the extract did not significantly change blood glucose levels. At 7th day, the highest mean blood glucose level was found in the control group, which was 462.40 ± 88.13 mg/ dl, followed by the Dragon Fruit Peel group-1 (327.60 ± 38.93 mg/ dl), 2 (284.20 ± 86.17 mg/dl), 3 (238.20 ± 84.74 mg/ dl), and the lowest was the standard group (152.00 ± 18.30 mg/ dl). Meanwhile, the blood glucose levels continued to decrease significantly on the 14th day. The highest blood sugar levels were found in the control group, namely 440.40 ± 100.98 mg/ dl, followed by the Dragon Fruit Peel Methanol-1 (203.80 ± 16.12 mg/dl), 2

(181.00 ± 19.71 mg/ dl), 3 (137.00 ± 24.75 mg/ dl), and the lowest glucose levels were found in the standard group, namely 133.20 ± 9.09 mg/ dl. Moreover, the percentage of blood glucose levels decreasing in the 7th and 14th days was described in Table 3.

Table 3. Percentage of Blood Glucose Level Decreasing in All Groups.

Group	Decreasing of Blood Glucose Level, ΔBGL (%)	
	7th day	14th day
Control	Reference	Reference
Standard	310.40 (67.13)	307.20 (69.75)
Dragon Fruit Peel Extract-1	134.80 (29.15)	236.60 (53.72)
Dragon Fruit Peel Extract-2	178.20 (38.54)	259.40 (58.90)
Dragon Fruit Peel Extract-3	224.20 (51.51)	303.40 (68.89)

Table 3 showed that the highest mean of blood glucose levels decreases on the 7th day was found in the standard group, which was 67.13%, followed by the Dragon Fruit Peel-3 (51.51%), 2 (38.54%), and the lowest was the Dragon Fruit Peel-1 (29.15%). Meanwhile, the mean decrease in blood glucose levels on the 14th day was not much different than on the 7th day. The highest mean of blood glucose levels decrease on the 14th day was found in the standard group, which was 69.75%, followed by the Dragon Fruit Peel-3 (68.89%), 2 (58.90%), and the lowest was the Fruit Peel Dragon-1 (53.72%). Furthermore, the distribution of blood glucose levels during this study was also described in Figure 1.

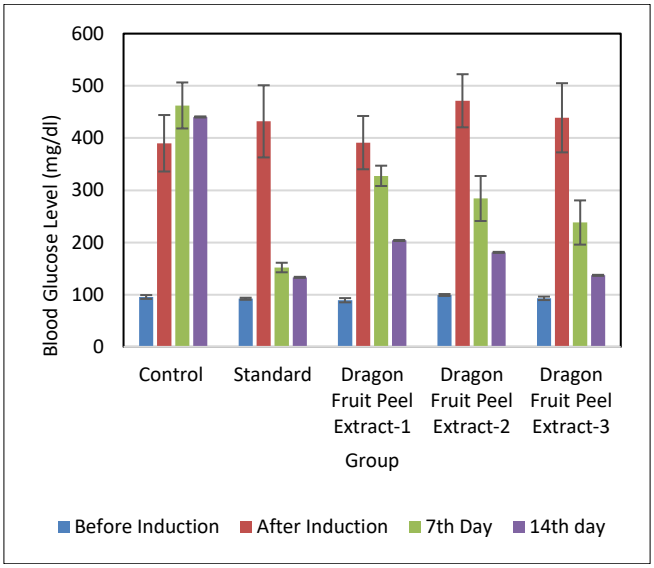

Figure 1. Bar Graph of Blood Glucose Level of All Groups during Observation.

Figure 1 showed that all groups showed the lowest mean blood glucose level before induction and the highest blood glucose level was found after induction. Only the control group showed an increase in blood glucose levels after treatment (7th and 14th day). At the end of the observation, all rats were sacrificed to obtain their pancreatic tissues for pancreatic histology study, which were described in Figure 2.

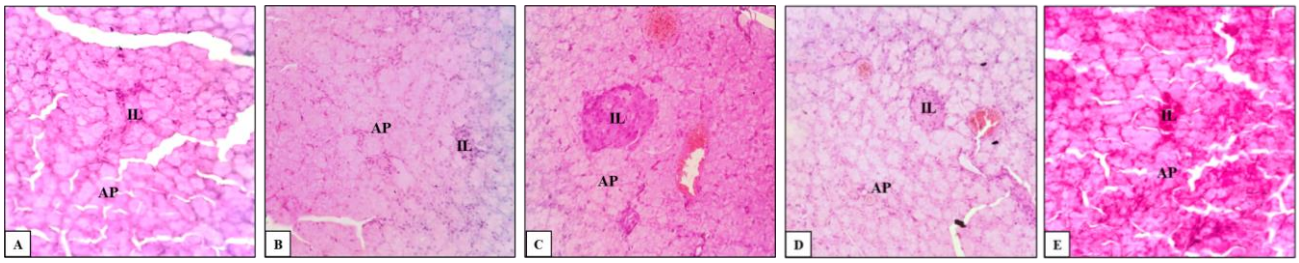

Figure 2. Pancreatic Tissue in All Groups. (A) Dragon Fruit Peel-1; (B) Dragon Fruit Peel-2; (C) Dragon Fruit Peel-3; (D) Standard; (E) Control. Staining: Haematoxylin and Eosin (HE)/Magnification: 400 x; Abbreviation: AP: Acini Pancreas; IL: Langerhans Islets.

Figure 2 showed some significant differences in the size and structure of the Langerhans islets in all groups. The control group did not receive the extract or standard treatment; the size of the Langerhans islets decreased, and an atrophic pancreatic Langerhans islet rose. It contrasted with the standard group, which showed an intact Langerhans islet. Meanwhile, the size of Langerhans islet increased in line with the dragon fruit peel extract increase. Interestingly, the highest dragon fruit peel extract dose revealed a similar pancreas tissue condition with the standard group. On the other hand, the lowest dragon fruit peel extract dose revealed a similar pathologic damage with a control group, which was an atrophic pancreatic Langerhans islet.

Based on the result above, dragon fruit peel extract yielded 4.22% with an antidiabetic effect, which can significantly decrease blood glucose levels seven days after treatment (P value < 0.05). The increase of dragon fruit peel extract did not significantly reduce the blood glucose level; it was concluded from the Post Hoc Test Tukey HSD in blood glucose level. However, the variation of dragon fruit peel extract dose significantly affects both the size and structure of the Langerhans islets. The highest dose of dragon fruit peel extract

revealed an intact Langerhans islet as well as the standard group in contrast to the lowest dose of dragon fruit peel extract, which revealed an atrophic pancreatic Langerhans islet and the control group.

This study used alloxan injection for diabetic induction. Alloxan is a urea derivate compound that induces Langerhans islet necrosis, especially beta cells. This necrosis occurs because of the autooxidation of alloxan radicals. Autooxidation destructs DNA structure and inhibits the thiol group of glucokinase enzyme, which decreases the formation of ATP and leads to reduced insulin secretion (Dewangan et al., 2017) (Ighodaro et al., 2017b) (Karthikeyan et al., 2016; Vijayaraj et al., 2019). Hence, it is obvious that alloxan could induce diabetic conditions, and the current study showed that after induction, all rats had blood glucose levels> 200 mg/ dl.

The current study result was in line with the previous study that the dragon fruit peel also had an antidiabetic activity. Solikhah et al. (2022) reported that dragon fruit peel ethanol extract had an antidiabetic effect on alloxan-induced diabetic mice. Solikhah et al. also reported that dragon fruit peel ethanol extract at 100 mg/kg BW and 300 mg/kg BW significantly decreased blood glucose levels on the first, seventh, and fourteenth days of treatment. This antidiabetic activity is due to the dragon fruit peel extract's flavonoid, terpenoid, tannin, polyphenol, quinone, and alkaloid. Saponins are reported to inhibit the α-amylase enzyme activity and have antioxidant effects. Polyphenols can inhibit the DPP-4 enzyme, increasing the half-life of GLP-1 and increasing insulin production through direct or indirect stimulation of pancreatic β cells. Polyphenols are also reported to increase peripheral tissue sensitivity to insulin and improve various diabetes complications such as kidney failure, vascular dysfunction, and other complications. Alkaloids can also act as PPAR γ agonists, increase glucokinase activity, and increase the expression of GLUT 4. Finally, flavonoids modulate the glucose transporter expression, especially GLUT-4 transporter, by increasing insulin secretion, reducing cell apoptosis, increasing the proliferation of pancreatic beta cells, and improving insulin resistance (Solikhah et al., 2022).

Another study performed by Panjaitan and Novitasari (2021) also reported a similar result to the current study. Panjaitan and Novitasari reported that ethanol extract of dragon fruit peel at a dose of 187.2 mg/ kg BW (37.44 mg/ 200 grams) and 374.4 mg/ kg BW (74.88 mg/ 200 grams) could significantly decrease blood glucose levels in streptozotocin-induced diabetic compared to the control group. The highest dose of dragon fruit peel extract (374.4 mg/ kg BW) significantly decreased the blood glucose levels that were as well as the standard group (Glibenclamide). It is due to phytochemicals, including tannins and flavonoids in the dragon fruit peel ethanol extract. Flavonoids and tannins are reported to have antioxidant effects that can facilitate decreasing blood glucose levels. The antioxidant effect of tannin can scavenge free radicals, inhibit glucose absorption in the gastrointestinal tract, and induce regeneration of pancreatic beta cells, leading to improved insulin sensitivity in adipose tissue and glucose uptake by insulin-mediated tissue. In addition, the antioxidant effect of tannin and flavonoids from dragon fruit peel extract also promotes protons donation to the alloxan radical as an induction compound in this study, thereby preventing further pancreatic damage, which leads to normalizing blood glucose level (Panjaitan & Novitasari, 2021).

The result of this study is in line with some previous studies that have been performed. Dragon fruit peel extract at the dose of 500 mg/ kg BW has shown antidiabetic activity, this dose was higher than the reported dose in the previous study. Panjaitan and Novitasari reported that the lower dose (374.4 mg/ kg BW) of dragon fruit peel extract had significantly decreased blood glucose levels. The current study also evaluated another parameter, histology of pancreatic tissue. Although the lowest dose of dragon fruit peel extract (500 mg/ kg BW) significantly decreased blood glucose level, it also showed an atrophic pancreatic Langerhans islet. Therefore, it showed that a lower dose of dragon fruit peel, which was 374.4 – 500 mg/ kg BW, significantly decreased blood glucose levels. Ironically, it required a higher dose to improve the pancreatic Langerhans islets.

CONCLUSIONS

Overall, it can be concluded that dragon fruit peel extract significantly decreased the blood glucose level, at least in the lowest dose (500 mg/ kg BW). However, it required a higher dose of dragon fruit peel extract to improve not only blood glucose level but also pancreatic Langerhans islet. Further study was required to evaluate safety and toxicity profile of dragon fruit extract to support the antidiabetic activity.

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