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Original Article

Anti-diabetic Activity of the Red Dragon Fruit Peel (*Hylocereus polyrhizus*) in Ethanol Extract against Diabetic Rats

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ABSTRACT

Background: The red dragon fruit peel, which is rarely used in general, contains higher antioxidant properties compared to the flesh parts and has various secondary metabolites utilised in medicines. **Objectives**: This study was aimed to determine the effects of ethanol extract administration of the red dragon fruit peel (*Hylocereus polyrhizus*) against the decline of blood glucose levels in diabetes mellitus rats. **Methods**: In this study, the total of 24 male white Wistar rats (*Rattus novergicus*) were divided into 4 groups. All experimental animals were induced to diabetic conditions by the administration of streptozotocin and nicotinamide dosages at 45 mg/kg body weight and 110 mg/kg body weight, respectively. For 14 days, each group was treated accordingly. The first group or negative control (NC) was treated with the administration of CMC-Na 0.5% dose 2 ml/200 g body weight; the second group or positive control (PC) was administrated with glibenclamide dose 0.09 mg/200 g body weight; the third (E1) and fourth (E2) groups were administered with the ethanol extracts of the red dragon fruit peels at dosages of 37.44 mg/200 g body weight and 74.88 mg/200 g body weight, respectively. **Results**: After the 14-day trial, the average levels of blood glucose on the negative control group (382.92 mg/dl) experienced no decline, and the blood glucose levels amongst groups were statistically different ($p<0.05$). **Conclusion**: The anti-diabetic activity of the red dragon fruit peel in the ethanol extract dose 74.88 mg/200 g body weight is statistically equal to the glibenclamide dose 0.09 mg/200 g body weight.
Key words: Antidiabetic activity, Diabetic rats, *Hylocereus polyrhizus*.

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INTRODUCTION

Diabetes mellitus is the leading cause in the developed countries and is one of the main health problems in the developing countries.[1] Diabetes mellitus is typically a disease that requires long-term medications and outstanding costs, mainly for the purchase of synthetic drugs. In fact, the use of synthetic medicines generally has negative impacts, such as hypoglicemia,[2] gastrointestinal disorders like nausea,[2] flatulent[3]; even the negative impacts of long-term use can cause kidney problems.[4-5] One of the methods to overcome the damaging collisions of the use of synthetic drugs is natural-based medicines, which can be used as an alternative choice in treating diabetes mellitus, which certainly have an anti-diabetic property.[6-7]

Relating to the anti-diabetic activities, some studies have showed diverse plants that are effective of decreasing blood glucose levels, such as soursop leaf (*Annona muricata*)[8]; the combination of *sirih merah* leaf (*Piper crocatum*) with *bawang dayak* (*Eleutherine palmifolia* Merr)[9]; Indonesian bay-leaf (*Syzygium polyanthum*)[10]; fenugreek seeds (*Trigonella foenum-graecum*)[11]; cinnamon (*Cinnamomum zeylanicum*) [11]; mangosteen skin (*Garcinia mangostana* Linn)[12](2); white dragon fruit (*Hylocereus undatus*) [13-14]; the red dragon fruit flesh (*Hylocereus polyrhizus*)[15-16], and the red dragon fruit peel (*Hylocereus polyrhizus*).[17]

Several findings reported that dragon fruit also develops various medicinal properties. The flesh of red dragon fruit is effective as an antioxidant. [18-20] Besides that, it has potential as *cardioprotective*,[21] *anti-cancer*,[20] *antibacterial*,[22] *anti-cholestrol*,[23] and *anti-diabetic*.[16,19] The results revealed that the flesh of red dragon fruit contains abundance secondary metabolites, such as betacyanin[24], flavonoid and phenolic[6,24], alkaloid, saponin, and tannin.[6]

To this extent, the use of red dragon fruit is only on its flesh, whereas the peels weighting for about 30-35% of the total fruit mass are not optimally exploited.[25] The phytochemical results demonstrated that the red dragon fruit peel contains some secondary metabolites, such as terpenoid[26] and alkaloid.[26,27] Moreover, it has contains tannin, steroid, and saponin[27,28], phenol hydroquinone, flavonoid, and triterpenoid.[28] The red dragon fruit peel is reported to have higher antioxidant activities compared to the flesh.[29,30] Previously, it was described that 1 mg/ml of red dragon fruit peel is effective of blocking free radicals of 83.48±1.02%, whereas its flesh is merely capable of 27.45±5.03%.[18] Furthermore, other studies relating to the red dragon fruit peel also mentioned that the administration of red dragon fruit peel-brewed water at 800 mg/ml may reduce blood glucose levels in rats.[17]

In the extraction process, the solvent is one of the essential parameters in the effectiveness of isolating bioactive compounds from a plant.[31] According to Agustiningsih *et al.* (2010)[32], the use of ethanol 96% as a solvent can optimally bind phenolic and flavonoid compounds compared to water or another combination of water and ethanol 96%. Accordingly, it is stated that the extraction process with the ethanol 96% solvent will produce an extract with a better total phenolic amount and antioxidant activity in comparison to extracts generated from a water solvent only. This is because ethanol is able to absorb more many compounds dissolved in a combination

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so that the extraction process with ethanol is more effective.[33] Relating to amounts and chemical substances extracted from the process, it was conducted in this study to evaluate the antidiabetic effectiveness of the red dragon fruit peel in ethanol extracts against diabetes mellitus rats induced by streptozotocin-nicotinamide (STZ-NA).

MATERIAL AND METHODS

Experimental animals

A total of 24 Wistar male white rats aged 2 months with the body weights of 154-257 g was collected from the laboratory of The Centre for Food and Nutrition Studies, University of Gadjah Mada, Yogyakarta, Indonesia. Before the trial begun, all experimental animals were adapted to the treated environment for 7 days. During the acclimatisation, all were fed with standard diet of comfeed-branded AD-II (PT JAPFA) and drunk *ad libitum*. The health condition was also observed by weighting the body weight. The implementation of this study was approved by the Ethic Commission of Health Research RSUD Dr. Moewardi, Solo, Indonesia with the *Ethical Clearance* No. 1.108/X/HREC/2019.

Extraction

Red dragon fruits were collected from the local farmers in Bakau Besar Laut Village, Sungai Pinyuh District, Mempawah Regency, West Kalimantan, Indonesia. The 50-day ripened red dragon fruits after the flowers blossomed were harvested for 15 kg and selected for better quality ones. After that, all were cleansed with flowing water and dried. The separation of the peels and flesh was conducted, and it was obtained the total wet weight of 5.83 kg. Next, the red dragon fruit peel was mashed using a blender and extracted by the maceration method. The extraction process referred to Putra's method (2013)[34]. The mashed red dragon fruit peels were then placed into a maceration vessel and soaked with 16 L of the distilled ethanol 96%. The extraction process was done 3x24 hours, and the extract solution was taken and stirred periodically for each 24 hours. The yield of red dragon fruit peels was filtered by filter papers, and the obtained filtrate was concentrated by *rotary evaporator* at 40˚C. The final extract was 30.01 g with a yield of 0.52%.

Manufacture of CMC-Na 0.5% solution

CMC-Na 0.5% solution was made accordingly the method of Salma *et al.*(2013)[35], and the dosage was defined by the references of Saputri & Zahara (2016).[36] A total of 0.5 g CMC-Na (Sigma-Aldrich) was poured into a beaker glass and dissolved in ±30 ml warm aquades, then was homogenously unified. CMC-Na solution was then moved to a 100 ml volumetric flask till reached the threshold and stirred up until homogenous. CMC-Na 0.5% solution dose 2 ml/200 g body weight was induced to experimental rats.

Manufacture of streptozotocin solution

Production of streptozotocin solution and dosages correspondingly referred to Ghasemi *et al.* (2014).[37] A total of 216 mg streptozotocin (Cayman Chemical) was dissolved in 72 ml buffer citrate with pH 4.5 which was prepared beforehand injection. Then, the homogenisation was performed by using homogeniser. Streptozotocin dose used in inducing diabetes mellitus in rats was 45 mg/kg body weight.

Manufacture of nicotinamide solution

Nicotinamide solution dose 110 mg/kg body weight was produced following the method of Ghasemi *et al.* (2014).[37] A total of 528 mg nicotinamide (Sigma-Aldrich) was suspended in 72 ml *sodium chloride* 0.9% (PT Widrata Bhakti). Nicotinamide dose110 mg/kg body weight was administrated to treated rats.

Manufacture of glibenclamide suspension

Production of glibenclamide suspension and dosage administration of 0.45 mg/kg body weight were correspondingly adopted from Salma *et al.* (2013).[35] Glibenclamide dosage (PT Indofarma) for adults is 5 mg. Hence, the dosage used in rats is 5 x 0.018 = 0.09 mg/200 g body weight. A glibenclamide tablet of 27 mg was placed into mortar for grinding, then was dissolved in 15 ml of CMC-Na 0.5% solution. Glibenclamide dosage administered to rats was 0.45 mg/kg body weight.

Rat Models with diabetes mellitus type 2

Experimental rats for diabetes mellitus type 2 were induced by using the combination of streptozotocin and nicotinamide dose 45 mg/kg body weight and 110 mg/kg body weight, respectively, in which was injected via intraperitoneal. Nicotinamide injection was given 15 mins before streptozotocin administration.[37]

Activity test of the red dragon fruit peel extracts

After all treated animals were adapted for 7 days, they were then randomly divided into 4 groups with each group of 6 rats. All rats were fasted for ±8-12 hours, and their blood was drawn for 0.5 ml via sinus orbitalis to measure the preliminary level of blood glucose (day 0). Also, on the same day, all rats were injected with the STZ-NA combination doses 45 mg/kg body weight and 110 mg/kg body weight via intraperitoneal. Nicotinamide injection was made 15 mins earlier than streptozotocin.[37] After 72 hours (day 3), the measurement of blood glucose level with STZ-NA induction was carried out. Rats are diagnosed with diabetes mellitus type 2 if the blood glucose levels > 200 mg/dl;[38] all rats used in this experimental study had blood glucose levels >200 mg/dl after STZ-NA administration. Afterwards, the extract was introduced once a day via oral for 14 days. The first group as negative control (NC) was administrated with the CMC-Na 0.5% solution dose 2 ml/200 g body weight; the second group as positive control (PC) was treated with glibenclamide dose 0.09 mg/200 g body weight; the third group was induced with the ethanol extract of red dragon fruit peel dose 37.44 mg/200 g body weight (E1); and the fourth group was injected with the ethanol extract of red dragon fruit peel dose 74.88 mg/200 g body weight (E2). The administration of ethanol extraction was initiated from day 4 to 17. On day 18, the blood was drawn back; yet, all rats were initially fasted for ±12-15 hours before the blood draw.

Measurement of blood glucose levels

A 0.5 ml blood sample was collected from sinus orbitalis using microhematocrit, then was inserted into eppendorf tube. The obtained blood sample was centrifuged at 4000 rpm for 15 mins. After that, the separated blood serum was taken out of 10 µl by microliter pipette and inserted into test tube. As a comparator, the standard test tube was added with 10 µl glucose standard FS (DiaSys). On the test tube with blood serum, it was added 1000 µl glucose reagent (Glucose GOD FS DiaSys) and homogenised by vortex. After homogenisation, the sample absorbance test was performed by using spectrophotometer UV at 500 nm. The results presented on the monitor were recorded on an observation sheet in mg/dl.

Data analysis

Overall, the data was statistically analysed using SPSS 24 for Windows. The data of average levels of blood glucose was then analysed using one-way analysis of variance, then was continued with the Duncan test at a confidence rate of 5%.

RESULTS AND DISCUSSION

The measurement of blood glucose levels was done three times; the initial blood glucose levels or before STZ-NA induction, the 72 hours

Table 1: Average levels of blood glucose in rats for each treatment group on day 0, day 3, and day18. Day 0 showed the initial blood glucose levels, day 3 showed the blood glucose levels after the administration of streptozotocin dose 45 mg/kg body weight and nicotinamide dose 110 mg/kg body weight, then day 18 showed the blood glucose levels after 14 days of the treatment extracts.

Trial Group	Average Levels of Blood Glucose (mg/dl)		
	Day 0	Day 3	Day18
NC	$73.78^{b} \pm 1.47$	$379.80^{a} \pm 30.87$	$383.92^{c} \pm 33.00$
PC	$70.73^{a} \pm 1.97$	$389.20^{ab} \pm 17.81$	$106.59^{a} \pm 3.11$
E1	$72.29^{ab} \pm 2.42$	$416.07^{b} \pm 20.14$	$140.62^{b} \pm 5.63$
E2	$70.39^{a} \pm 2.32$	$401.13^{ab} \pm 20.18$	$109.17^{a} \pm 2.60$

Information:

NC = Negative Control (CMC-Na 0.5% solution dose 2 ml/200 g body weight)

PC = Positive Control (glibenclamide dose 0.09 mg/200 g body weight)

E1 = Administration of ethanol extract of the red dragon fruit peel dose 37.44 mg/200 g body weight

E2 = Administration of ethanol extract of the red dragon fruit peel dose 74.88 mg/200 g body weight

*Numbers shown after ± demonstrated SD (standard deviation)

*Group followed by the same letters are not significantly different (p>0.05)

blood glucose levels after STZ-NA induction, and overall blood glucose levels after the 14-day treatments. In the measurement of the initial blood glucose levels, all rats had normal rates; after STZ-NA injection, all blood glucose levels in rats increased; after the treatments for 14 days, the positive and extract-treated groups experience declines (Table 1).

Diabetes mellitus is a metabolic disorder with a sign of high glucose levels in blood, as a result of pancreatic impairment due to inactivity of producing insulin at optimal levels or our body is not able to use insulin effectively. The decline in the functions of pancreas as an insulin producer causes disruptions in the metabolism of carbohydrates, lipids, and proteins which can lead to hyperglycaemia condition. Therefore, one of the methods that can be done to diagnose diabetes mellitus is by measuring blood glucose levels.

Based on Table 1, it was seen, on day 0 (before STZ-NA induction), the blood glucose levels in the experimental rats were normal (70.39-73.78 mg/dl). Following with Wolfenshon & Lloyd (2013),[39] it was stated that the blood glucose levels in fasting rats are approximately 50-135 mg/dl. Furthermore, this study reported that on day 3 (72 hours after STZ-NA induction), the blood glucose levels in the treated rats were above 200 mg/dl, ranging from 379.80-416.07 mg/dl, which indicated that all rats were diabetes mellitus. In accordance with Anwer (2014)[38]; Nurhidajah & Nurrahman(2016),[40] it was demonstrated that blood glucose levels would be >200 mg/dl after 72 hours STZ-NA administration, and it can be claimed that rats were in diabetes mellitus type 2 already.

Streptozotocin is a compound which works by forming highly reactive free radical exposure so that can cause damages to cell membranes, proteins, and DNAs, including disruptions in insulin production in pancreatic β-cells. Streptozotocin (STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose) can enter cytoplasm of pancreatic β-cells through glucose transporter 2 (GLUT 2) which exists on plasma membranes.[41-42] Glucose group on streptozotocin structure which activates toxic effects on streptozotocin is more selective against pancreatic β-cells, and this can easily make streptozotocin entering pancreatic β-cells because they are more active seizing glucose compared to other cells.[43] After entering, streptozotocin will trigger DNA alkylation.[42,44] *Methylnitrosurea* from streptozotocin structure is responsible for toxicity activity owned by streptozotocin over the formation of methyl carbonium ions (CH^{3+}), which is extremely reactive producing methylation and DNA fragmentation.[37] The incoming streptozotocin is then metabolised by cells and becomes a donor for the formation of *nitric oxide* (NO) which contributes to cell damages within the increased activity and the release of free radicals.[45] This emerges the binding of reactive oxygen in mitochondria, inhibition of Krebs cycle, and degeneration of oxygen consumption in mitochondria, cutback of ATP production and nucleotides in pancreatic β-cells,[46] and eventually inhibition of secretion and insulin synthesis[45] so that blood glucose levels cannot enter into cells appropriately and result in hyperglycaemia which lead to diabetes mellitus type 2.[47]

The administration of the combination of streptozotocin and nicotinamide can prevent from excessive hyperglycaemia and mortality in rats. Nicotinamide is an antioxidant derivate vitamin B3 (Niacin) which protects pancreatic β-cells from cytotoxic activity of streptozotocin in several mechanisms.[37,48] Nicotinamide can stimulate the regeneration of pancreatic β-cells, the growth of Langerhans cells, and can block apoptosis reactions. Besides that, the nicotinamide administration before streptozotocin injection can act as an acceptor of methyl group so that can reduce the DNA methylation process in pancreatic β-cells.[37]

After the treatments for the 14 consecutive days from day 4 to 17, it was recorded the decline of blood glucose levels in the groups of PC, E1, and E2, ranging from 106.59–140.62 mg/dl; yet, it was conversely in NC. As stated by Dewi *et al.* (2016),[49] CMC-Na is neutral, then the administration of CMC-Na solution in this study was not also adequately effective in inducing anti-diabetic activity, which marked in the decrease of blood glucose levels.

Glibenclamide is one of the sulfonylureas class drugs, which is commonly used for therapies in patients with diabetes mellitus type 2.[50] Glibenclamide is used either in a single or combination medication that can lower blood glucose levels effectively.[51] The mechanism action of glibenclamide is to increase the release of insulin hormone in Langerhans pancreatic β-cells.[44] Sulfonylureas work by hindering K^{+} channels from pancreatic β-cells through sulfonylurea receptors that block the channels of ATP-sensitive K^{+}.[52] This inhibition causes membrane depolarisation, and this condition will open Ca channels. While opening Ca channel, Ca^{2+} ions will enter into pancreatic β-cells, stimulate the granules containing insulin, and insulin secretion occurred via exocytosis.[53]

The red dragon fruit peels have been reported to develop a greater amount of phenolic in comparison with their flesh.[29] This study suggested that the ethanol extract of the red dragon fruit peel was able to reduce blood glucose levels significantly. The effectiveness is related to the secondary metabolites contained in the filtrate extraction of the red dragon fruit peels. As also stated, the red dragon fruit peel holds various secondary metabolites[26-28] and antioxidant property;[29,30]

the previous studies demonstrated that the brewed water of the red dragon fruit peel has anti-diabetic activity.[17] The aim of ethanol extraction in this study was to ensure all the filtrates properly filtered and concentrated following the method of Agustiningsih *et al.* (2010),[32] in which stated that the use of ethanol 96% as a solvent could bind optimally all compounds of phenolic and flavonoid in comparison with water or another solvent combination of water and ethanol 96%. Likewise, Rivai *et al.* (2013)[33] revealed that the extractions with ethanol 96% produce a better total amount of phenolic and antioxidant activity compared to water solvent. Ghasemzadeh & Ghasemzadeh (2011)[54] exposed that the compounds of phenolic and flavonoid have a linier contribution upon antioxidant activities so that the higher amounts of phenol and flavonoid in an extraction, the better antioxidant activity. Not only that, the reduction of blood glucose levels in rats due to the administration of ethanol extract of the red dragon fruit peel also does a result of the antioxidant properties belong to the red dragon fruit peels; the previous studies reported that the ethanol extraction in the red dragon fruit peel has high antioxidant, which is flavonoid.[27,28,55] Flavonoid plays a role in donating hydrogen atoms so that it will be oxidized and bound to free radicals, making them more stable.[13] Aside from flavonoids, the red dragon fruit peel also comprises tannin.[27-28] Tannin is a phenolic compound that acts as an antioxidant.[56] The mechanism action of tannin as an antioxidant is to catch free radicals, to hinder the glucose absorption in intestinal, to induce the regeneration of pancreatic β-cells that impacts on adipose cells to strengthen the insulin activity, and to improve glucose intake in the blood through the activity of insulin mediator resulting in the reduction of glucose levels in blood.[56]

CONCLUSION

The ethanol extraction of the red dragon fruit peel may decline blood glucose levels in rats with diabetes mellitus, and the anti-diabetic activity of the red dragon fruit peel dose 74.88 mg/200 g body weight is statistically equal to glibenclamide dose 0.09 mg/200 g body weight.

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GRAPHICAL ABSTRACT

Anti-Diabetic Activity

Average levels of blood glucose in rats on each treatment group on the day 0,3, and 18

Trial Group	Average Levels of Blood Glucose (mg/dl)		
	Day 0	Day 3	Day 18
NC	$73.78^{b} \pm 1.47$	$379.80^{a} \pm 30.87$	$383.92^{c} \pm 33.00$
PC	$70.73^{a} \pm 1.97$	$389.20^{ab} \pm 17.81$	$106.59^{a} \pm 3.11$
E1	$72.29^{ab} \pm 2.42$	$416.07^{b} \pm 20.14$	$140.62^{b} \pm 5.63$
E2	$70.39^{a} \pm 2.32$	$401.13^{ab} \pm 20.18$	$109.17^{a} \pm 2.60$

Information:

NC = Negative Control (CMC-Na 0.5% solution dose 2 ml/200 g body weight)

PC = Positive Control (glibenclamide dose 0.09 mg/200 g body weight)

E1 = Administration of ethanol extract of the red dragon fruit peel dose 37.44 mg/200 g body weight

E2 = Administration of ethanol extract of the red dragon fruit peel dose 74.88 mg/200 g body weight

*Numbers shown after ± demonstrated SD (standard deviation)

*Group followed by the same letters are not significantly different (p>0.05)

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