



## Antidiabetic of *Hylocereus polyrhizus* peel ethanolic extract on alloxan induced diabetic mice

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### Abstract

Diabetes is a disease characterized by high blood glucose due to the abnormal response of the cells in the body on produced insulin or insulin resistance. Indeed, the treatment for diabetes mellitus lasts for a lifetime and causes various side effects, such as headache, hypoglycemia, vomiting, and gastrointestinal symptoms. Interestingly, Dragon fruit has potent antidiabetic activity and without side effects. Thirty Wistar mice were included in the study. Alloxan with a dose of 150 mg/kg was injected intraperitoneally to all groups except the standard control group. Mice with blood glucose levels higher than 200 mg/dL were considered diabetic and employed throughout the study. Mice were divided into five groups: standard control group without alloxan, diabetic control group with alloxan, treatment group of 100 mg/kg and 300mg/kg *H. polyrhizus* peel extract, and positive control group with 600 µg/kg glibenclamide. All treatments were given orally. Blood glucose level was checked on day 1, 7, and 14 on all groups using Accu-check instant glucometer. This study revealed that administration of alloxan to the diabetic control group significantly increased blood glucose level compared to the normal control group on day-1, 7, and 14 ( $P < 0.05$ ). In addition, administration of *H. polyrhizus* peel extract and glibenclamide effectively decreases blood glucose levels, especially on day-7 and 14 compared to the control group ( $P < 0.05$ ).

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### Introduction

Diabetes is a disease characterized by high blood glucose due to the abnormal response of the cells in the body on produced insulin (1). Insulin is a hormone that enables human cells to absorb glucose and convert it into energy. If the body does not absorb glucose, it will accumulate in the blood (hyperglycemia), which leads to various potential medical complications (2,3). Diabetes mellitus can cause multiple organ dysfunction, typical symptoms such as

polyuria, weight loss, blurred vision, and metabolic disorder that increase by the year (4,5).

A diabetic patient will need constant monitoring to ensure their blood sugar level is typical to lessen the probability of complication. Diet and physical activity are important factors in controlling diabetes. To date, the treatment for diabetes mellitus lasts for a lifetime and causes various side effects, such as headache, hypoglycemia, vomiting, and gastrointestinal symptoms. Some common oral medications for diabetes include alpha-glucosidase

inhibitors, biguanides, meglitinib, sulfonyleureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitor (6,7).

Therefore, it is necessary to find alternative antidiabetic drugs that are natural (8-10). One of the plants beneficial as antidiabetic is the dragon fruit. Pitaya or Red dragon fruit (*Hylocereus polyrhizus*) is a cactus family vine (Cactaceae). Pitaya, called dragon fruit, is a cactus with epiphytic and terrestrial traits. This dragon fruit plant requires support poles or other trees (11). The part of dragon fruit that can be utilized as antidiabetic medicine is the peel (reference). Red Dragon peel, known as (*Hylocereus polyrhizus*), contains beneficial ingredients for the human body such as flavonoids, polyphenolic, anthocyanins, isorhamnetin glucoside, rutin, quercetin hexoside, kaempferol glucorhamnoside, isorhamnetin, and galloylglucoside (12). Unfortunately, most people only consume the flesh of the dragon fruit. Red dragon fruit skin is a rarely used waste. Even though red dragon fruit skin also contains antidiabetic substances, i.e., high flavonoid and alkaloids. One way to utilize dragon fruit skin is by extracting it for the main ingredient of various functional foods beneficial as an antidiabetic medicine (reference).

Several previous studies stated that dragon fruit could be used as antidiabetic medicine, including study (13), which showed that water extract from dragon fruit obtained by maceration significantly reduced blood glucose level and controlled oxidative damage in diabetic mice induced by Streptozotocin. Another study (14) also presented that white dragon fruit had an antidiabetic effect on diabetes mellitus patients by inhibiting the phosphodiesterase enzyme GLUT2 and reducing oxidative stress. Compared to previous studies, the research that we will examine is not the fruit, but the skin, because dragon fruit skin is a waste that is usually thrown away for free. So, in this study, we will use dragon fruit skin for antidiabetic treatment. This study aims to identify the effectivity of red dragon fruit skin as antidiabetic on alloxan-induced mice is conducted using different ingredients and variations of doses from previous studies.

## Materials and methods

### Animals

Adult male mice (*Mus musculus L.*), aged approximately three months and weighing between 25-35 grams, were utilized in this study. Mice were put in a plastic cage covered with wire mesh. A layer of 1 cm husk used to cover the cage's bottom was changed every two days. The intensity of light, humidity, and room temperature were adjusted. Ethical code, institutional, and national regulation of live animals were rigorously followed, and the Health Research Ethical Clearance, Faculty of Dental Medicine, Airlangga University, granted ethical clearance for the animals used in this inquiry (Reg No. 453/HRECC.FODM/VII/2021).

### Concoction of extract

*H. polyrhizus* peel was dried in the oven at 60°C. The peel was then made into powder with a grinder. A mix of 1:7 *H. polyrhizus* peel powder was mixed in 96% ethanol and let sit at room temperature for 2 hours. Subsequently, the mix was filtered, and maceration was separated and re-macerated with 96% ethanol with a ratio of 1:4. All maceration was evaporated at 60°C after filtering till it became a thick extract. The solvent used to dilute the extract into desired concentration was Carboxyl Methyl Cellulose (CMC).

### Flavonoid test

A formula of hydrochloric alcohol from a mixture of 2 mL amyl alcohol, Mg powder, and 5 mL of *H. polyrhizus* peel extract was mixed thoroughly and let sit to separate. A positive result was obtained if there was a formation of the yellow amyl alcohol layer.

### Tannin test

A solution of *H. polyrhizus* peel extract was mixed with a steady reagent and heated in a water bath to acquire a pink deposit. The by-product was filtered and saturated with NaCl, and then gelatin was added. A positive result was obtained if a white deposit was formed.

### Alkaloid test

A mix of 2 mL *H. polyrhizus* peel extract and 50 mL of water was heated for 5 minutes and filtered. Mayer and Dragendorff tests were carried out by adding 5 mL of *H. polyrhizus* peel extract into a reaction tube. A positive result was obtained if there is a formation of white deposit in the Mayer test and an orange deposit in the Dragendorff test.

### Saponins test

10 mL of *H. polyrhizus* peel extract was added into the reaction tube, then shaken for 10 seconds, and let still for 10 minutes. A positive result was obtained if there was an accumulation of bubbles or foam.

### Polyphenol test

5 mL of *H. polyrhizus* peel extract was mixed with three drops of FeCl reagent. A positive result was obtained if a blue-green color was formed.

### Quinone test

5 mL of *H. polyrhizus* peel extract were mixed with 1 N NaOH. A positive result was obtained if there was a formation of red color.

### Steroids and Terpenoid test

5 mL ether solution of *H. polyrhizus* peel extract was evaporated, and one drop of thick H<sub>2</sub>SO<sub>4</sub> and two drops of anhydrous acetic acid were added to the residue. A positive result for steroids was obtained if there was a formation of

green color. A positive result for terpenoid was obtained if there was a formation of brown color.

#### Acute toxicity test (LD50)

The acute toxicity test was performed to determine the toxicity of *H. polyrhizus* peel extract. This test is vital to evaluate the characteristics that can be toxic from a chemical substance. The information from this test can be given to humans about the danger of short-term orally exposed chemicals (15,16). 150 mg/kg and 300 mg/kg of *H. polyrhizus* peel extract were given orally to 6 male mice and observed every 6 hours for 48 hours to confirm non-toxicity.

#### Antidiabetic test

Mice were separated into five groups consisting of 6 mice. Type 1 diabetes was induced in mice with alloxan. Alloxan was dissolved in a NaCl of 0.9%, and a dose of 150 mg/kg was injected intraperitoneally to all groups except normal control group. Five days post-injection, blood glucose levels in mice were tested with a glucose kit. Mice with fasting glucose levels  $\geq 200$  mg/dL were considered diabetic and were used in this study. Mice were divided into a normal control group without alloxan, diabetic control group with alloxan, extract treatment group of 100 mg/kg and 300mg/kg *H. polyrhizus* peel extract, and positive control group with 600  $\mu$ g/kg Glibenclamide. All treatments were given orally. Blood glucose level was checked on day 1, 7, and 14 on all groups using Accu-check instant glucometer (17).

#### Data analysis

All data in this study were analyzed with SPSS ver. 22. Two-way ANOVA was used to investigate its significance. Differences were deemed significant if *P* value < 0.05.

#### Results

##### Phytochemical screening of *H. polyrhizus* peel extract

*H. polyrhizus* peel extract is shown to contain saponin, flavonoid, tannin, polyphenol, alkaloid, quinone, and terpenoid, as listed in Table 1.

##### Acute toxicity test (LD<sub>50</sub>)

Single-dose (150 and 300 mg/kg body weight) of *H. polyrhizus* peel extract were given orally to diabetic mice for 48 hours with no mortality observed.

##### Antidiabetic effect of *H. polyrhizus* peel extract on blood glucose level

This study shows that administration of alloxan to the diabetic control group significantly increased the blood glucose level compared to the normal control group on day-1, 7, and 14 (*P*<0.05). The mean increase was 41.4 mg/dl. Administration of glibenclamide and *H. polyrhizus* extract

decreases blood glucose levels, especially on day-7 and 14 compared to the diabetic control group (*P*<0.05). On the seventh day, the 300 mg/kg extract treatment group showed the highest decrease in blood glucose, significantly different from the glibenclamide and the 150 mg/kg extract treatment. While on the 14th day, the 300 mg/kg extract treatment group was not significantly different from the glibenclamide treatment but significantly different from the 150 mg/kg extract. The result of the Antidiabetic effect of *H. polyrhizus* peel extract on blood glucose level can be seen in table 2.

Table 1. Phytochemistry of *H. polyrhizus* peel extract

Chemical Substance	Result
Saponins	+
Flavonoids	+
Tannins	+
Polyphenol	+
Alkaloids	+
Quinone	+
Steroids	-
Terpenoids	+

(+) positive result and (-) negative result.

#### Discussion

Mice were injected using alloxan. Alloxan is one of the many agents frequently used to evaluate the antidiabetic potential of a pure compound or plant extract in research concerning diabetes. A single dose of alloxan (150 mg/kg body weight) injected intraperitoneally is shown to be largely successful in inducing diabetes in 80% of animal subjects with only a 10% mortality rate. The hyperglycemic effect is only made within 2-3 days by alloxan. Alloxan can affect the quality and quantity of insulin produced by pancreatic beta cells. Alloxan exhibits its pathological effect via glucokinase inhibition and reactive oxygen species cycle generation after it manages to enter pancreatic beta cells (18). The depolarization process was involved in the pancreatic beta cells, facilitating further calcium entry via voltage-dependent calcium channels into pancreatic cells. The level of Ca<sup>2+</sup> is high in the intracellular. This condition has been noted to significantly contribute to the super high level of insulin release (19).

The administration of a single dose of *H. polyrhizus* peel extract (150 and 300 mg/kg BW) and glibenclamide (600  $\mu$ g/kg BW) for 14 days showed a decrease in blood glucose levels. Based on its effectiveness, dragon fruit peel extract at a dose of 300 mg/kg was as effective in lowering blood glucose as the administration of glibenclamide. Dragon fruit peel has been shown to reduce blood glucose levels in diabetic mice. The benefits of Dragon fruit peel are believed to encourage the growth of pancreatic cells to produce insulin. It was also found that the higher the dose of dragon

fruit peel they consumed, the more significant the decrease in blood glucose levels they received.

Glibenclamide is an oral drug classified as sulfonylurea, used as an antidiabetic drug (15,20,21). In patients with hyperglycemia, this drug works by stimulating insulin production from pancreatic beta cells (22). Glibenclamide

binds to the sulfonylurea receptor 1, the ATP-sensitive potassium channel regulatory subunit (KATP) found in pancreatic beta cells. The cell membrane will be depolarized, and calcium channels will open. This causes the intracellular calcium concentration to increase inside the beta cells and stimulates insulin release (23,24).

Table 2: Effects of *H. polyrhizus* peel extract on blood glucose level *H. polyrhizus* peel extract on blood glucose level

Group	Day 1	Day 7	Day 14
Negative control	110±7.90	104.6±5.89	112.6±8.38
Diabetic control	354.2±8.78	378.2±12.15	395.6±9.39
<i>H. polyrhizus</i> peel extract 150 mg/kg body weight	361±12.31	215.5±10.75	140.25±6.87
<i>H. polyrhizus</i> peel extract 300 mg/kg body weight	366.2±4.43	159.6±11.43	122.6±5.59
Glibenclamide	354.2±5.40	219.80±5.58	111.80±8.92

Values are expressed as mean±SD.

This study found that the ethanol extract of Red Dragon Fruit peel (*H. polyrhizus*) contains some chemicals that play a role in lowering blood glucose levels, such as saponins, flavonoids, terpenoids, tannins, polyphenols, quinones, and alkaloids. Saponins can inhibit diabetes by reducing hyperglycemia levels. The mechanism of lower blood sugar levels of saponins is through insulin rejuvenation, changes in insulin signaling, the insulin release from beta cells, inhibition of disaccharide activity, activation of glycogen synthesis, inhibition of gluconeogenesis, inhibition of glucosidase activity, inhibition of mRNA expression of glycogen phosphorylase and glucose 6-phosphatase and increased expression of GLUT4 (25).

Saponin was found to be active in inhibiting alpha-amylase. In addition, there is an increased reduction activity by saponin as a potential antioxidant (26). The effect of tannin compounds is as an antihyperglycemic agent (27). Polyphenols were found to have antidiabetic potential as they inhibit dipeptidyl peptidase-4 that led to the increase of glucagon-like peptide-1 half-life, increased insulin production through direct or indirect  $\beta$ -cell stimulation, and increased insulin sensitivity on peripheral tissue (28), but it also improves due to diabetes complications such as kidney failure, vascular dysfunction, and others (29). Alkaloids play a role in the antidiabetic effect by causing peroxisome PPAR $\gamma$ , glucokinase activity, and an increase in GLUT4 (30,31). The role of terpenoids in the treatment of diabetes is to activate the AMPK fuel-sensing enzyme (Adenosin monophosphate protein kinase (AMPPK)). Active AMPPK causes an increase in blood pressure and blood glucose homeostasis in insulin-resistant rats (32). The antidiabetic effect of flavonoids can be seen from their modulating effect on blood sugar transporters. This occurs through the mechanism of increasing insulin secretion, reducing the process of apoptosis, increasing pancreatic cell proliferation, reducing insulin resistance, and increasing GLUT4

translocation through the PI3K/AKT and AMPK pathways (33).

According to a study, Quercetin, Anthocyanin, Betacyanin, Chlorogenic Acid, and Gallic Acid are all antidiabetic substances found in dragon fruit peel (34). Quercetin is a flavonoid colorant commonly found in fruits, leaves, and flowers. Quercetin has been demonstrated to have a significant antidiabetic effect in addition to its ability to provide color. There are numerous processes by which quercetin reduces blood glucose levels, including quercetin's antioxidant activity, which can protect pancreatic cells from oxidative stress and aid enhance insulin secretion (35). Quercetin can also boost circulating adipokine, inhibit glucosidase activity in the small intestine, and boost the GLUT4 transporter in skeletal muscle (36).

Besides quercetin, another compound in the skin of red dragon fruit that has an antidiabetic effect is anthocyanin. Anthocyanins are dyes that are found in many fruits and vegetables. A study proved that anthocyanins have a hypoglycemic effect by preventing damage to pancreatic cells to increase insulin secretion. Anthocyanins can also increase the circulation of GLUT4 in the plasma membrane in skeletal tissue and the heart so that glucose absorption increases (37). Another dye also found in the skin of red dragon fruit is betacyanin. Fresh red dragon fruit peel extracted with methanol pH 5 contained betacyanin (515.20 g/100 g) higher than the content extracted in water pH 5 (491.16 g/100 g). Betacyanin has been shown to improve insulin sensitivity. In addition, betacyanin can also increase adipokine production, which plays a role in glucose regulation and fatty acid oxidation (38).

Compounds also found in the peel of *H. polyrhizus* are chlorogenic acid and gallic acid (39). The chlorogenic acid found in red dragon fruit peels also exhibits a hypoglycemic effect by stimulating glucose absorption and increasing insulin sensitivity. Gallic acid exerts an antidiabetic effect by increasing glucose for energy and increasing insulin

sensitivity. In addition to antioxidants, red dragon fruit skin also contains high dietary fiber, reducing blood glucose levels. Red dragon fruit peel has a fiber content of 69.3% with a composition of 56.50% water-soluble fiber and 14.82% water-insoluble fiber (40).

## Conclusion

The compounds contained in the *H. polyrhizus* peel extract include saponins, flavonoids, tannins, polyphenols, alkaloids, quinone, and terpenoids. The extracts had no toxic effect even in a dose of 2000 mg/kg body weight. The administration of *H. polyrhizus* (150 mg/kg and 300 mg/kg) peel extract and glibenclamide lowered blood glucose levels in diabetic mice induced by alloxan. *H. polyrhizus* peel extract can be used as an alternative medicine for diabetes. Further study of antioxidant activity of *H. polyrhizus* peel extract in combination with specific gene expression or biomarkers related to diabetes is needed to understand the effect on a diabetic patient.

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## Authors' Contributions

Tridiganita Intan Solikhah supervised the experiment. He conducted the study along with Cinta Atsa Mahesa Rani, Mela Septiani, and Yan Arengga Syah Putra. All authors read and approve the final manuscript.

## Conflict of Interest

The authors declare no conflicts of interest.

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## مضاد داء السكري للمستخلص الايثانولي لقشور *Hylocereus polyrhizus* على الفئران المصابة بداء السكري المستحدث بالألوكسان

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### الخلاصة

يمتاز داء السكري بارتفاع سكر الكلوغوز في الدم نتيجة للاستجابة غير الطبيعية لخلايا الجسم في إنتاج الانسولين او مقاومة الانسولين. ان علاج داء السكري قد يستمر مدى الحياة مسببا آثارا جانبية كالصداع و نقص سكر الكلوغوز في الدم و القيئ و اعراضاً للجهاز الهضمي. من المثير للاهتمام ان فاكهة التنين تمتاز بنشاط قوي مضاد لداء السكري من دون اعراض جانبية. تم استخدام ثلاثون فأرا من نوع ويستر في الدراسة، و تم حقن جميع المجاميع بالألوكسان بجرعة ١٥٠ ملغم/كغم في الخلب ماعدا مجموعة السيطرة القياسية. تم اعتبار الفئران التي يرتفع مستوى كلوكوز الدم عن ٢٠٠ ملغم/ديسليتر مصابة بداء السكري و هي التي تم استخدامها في الدراسة. قسمت الفئران إلى خمس مجموعات: مجموعة السيطرة القياسية بدون الألوكسان، مجموعة السيطرة المصابة بداء السكري بالألوكسان والمجموعتان المعاملتان بجرعة ١٠٠ و ٣٠٠ ملغم/كغم من مستخلص قشور *H. polyrhizus* و مجموعة السيطرة الموجبة المعاملة بالكلابينكلامايد ٦٠٠ مايكروغرام/كغم. جميع المجاميع تم تجريعها عن طريق الفم. تم فحص مستوى كلوكوز الدم في الايام ١ و ٧ و ١٤ للمجاميع كافة باستخدام جهاز قياس السكري الفوري-Accu-check. أظهرت هذه الدراسة أن إعطاء الألوكسان لمجموعة السيطرة لمرض السكري أدى إلى زيادة معنوية في مستوى الكلوغوز في الدم مقارنة بمجموعة السيطرة القياسية في اليوم الأول و السابع والرابع عشر عند مستوى احتمالية ( $P < 0.05$ ) فضلا عن ذلك، فإن تناول مستخلص قشر *H. polyrhizus* و الكلابينكلامايد يقلل بشكل فعال من مستويات الكلوغوز في الدم و خاصة في اليوم السابع والرابع عشر مقارنة بمجموعة السيطرة عند مستوى احتمالية ( $P < 0.05$ ).