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Association between extract from fruit of *Opuntia ficus-indica* and streptozotocin-induced diabetic rats

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Opuntia ficus-indica has traditionally been used in prevention and treatment of various diseases such as diabetes mellitus. The current study was performed to determine whether *Opuntia ficus-indica* is associated with diabetes. Diabetic rat models were induced with streptozotocin (STZ). This study divided rats into 1 day (short-term) and 4 consecutive weeks (long-terms) of daily administration. These groups were subdivided into four groups each other for assessment of blood glucose level as follows: Group 1, untreated rats given distilled water; Group 2, untreated rats given *Opuntia ficus-indica*; Group 3, STZ-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*. Blood glucose level was measured for one day and four weeks. In addition, serum markers of alanine aminotransferase (ALT), aspartate transaminase (AST), cholesterol, and creatinine were determined, and total protein triglycerides were measured at four weeks. Blood glucose level was highest in both groups (Group 3 and Group 4) at 30 minutes and two weeks and gradually decreased in a time-dependent manner. The difference in blood glucose among the four groups was significant ($p < 0.05$). Additionally, the levels of ALT, AST and triglycerides were significantly decreased by *Opuntia ficus-indica*.

Keywords: *Opuntia*; diabetes mellitus; blood glucose; alanine transaminase; aspartate aminotransferases

Introduction

The Cactaceae family is reported to contain about 130 genera and nearly 1,500 species. It is distributed in arid and semiarid environments, particularly during prolonged dry spells. Due to efficient use of water, the carbon dioxide fixation pathway of cacti called crassulacean acid metabolism (CAM) allows greater conversion of water to dry matter [1,2]. The Cactaceae family is widely distributed in Mexico and in all American hemispheres, Africa, the Mediterranean basin, Australia, and India [3]. The cactus *Opuntia ficus-indica*, commonly known as prickly pear, belongs to the family Cactaceae and produces nutritionally rich and sweet fruits. The prickly pear cactus is a member of the *Opuntia* genus and also is known as the nopal, tuna, and sabra. Its fruits and stems are eaten due to richness of elements including fiber, minerals, vitamins, fatty acids, sugars, polyphenols, and flavonoids. It is also used in various products including food, fodder for cattle, raw material for preparing plywood, soap, dyes, adhesives and glue, and cosmetics such as shampoo, cream, and body lotions [1-4].

Diabetes mellitus (DM) is a disease that seriously threatens human health, with more than 200 million people suffering from the disease worldwide. The World Health Organization (WHO) estimates that the number of patients with diabetes will exceed 360 million by 2030 [5]. In the United States, the diabetic population is expected to comprise one-third of all adults by 2030 [6]. DM is an insistent metabolic disorder characterized by hyperglycemia, hypertriglyceridemia, and hypercholesterolemia [7]. In particular, chronic elevation of blood glucose can cause not only DM, but also various diseases such as kidney failure, blindness, stroke, heart attack, and death [8]. Treatments for diabetes include diet therapy, exercise therapy, and pharmacotherapy including α -glucosidase inhibitors, insulin, sulphonylurea, biguanide, and troglitazone. Despite recent efforts to treat DM, drug treatment is an imperfect therapy with side effects. In recent reports, some plants such as *hemerocallidea corm*, *Sanguis draxonis*, and *Opuntia ficus-indica* showed possibility for treatment of DM [9].

Opuntia ficus-indica has traditionally been used to manage conditions including diabetes, lipid disorders, cancer, inflammation, ulcers, and reduced blood glucose level [10,11]. However, scientific knowledge about and the specific functions of *Opuntia ficus-indica* are unclear.

The aim of this study was to investigate the correlation between *Opuntia ficus-indica* and DM and to suggest the possibility of *Opuntia ficus-indica* use in prevention and treatment of DM.

Materials and Methods

Plant

The *Opuntia ficus-indica* utilized for purposes of the current study was purchased from Cactus Infusion Corporation (Korea). The fruit of *Opuntia ficus-indica* was extracted by high pressure and stored at 4°C until use.

Animals

Sprague-Dawley rats weighing 200 to 250 g were selected and used for this study. They were housed in standard environmental conditions (12:12 h light/dark cycle, 25°C \pm 3°C, 40% to 60% humidity). All experimental designs and procedures were approved by the Institutional Animal Care & Use Committee of The Catholic University of Korea (YEO2017310102FA).

DM was induced experimentally in rats using streptozotocin (STZ) (Sigma SO130; USA) dissolved in 0.4 M sodium citrate buffer (pH 4.5) injected into the abdominal cavity (65 mg/kg body weight) [12]. After injection, rats were allowed to stabilize

for seven days. At eight hours of fasting, blood glucose concentration was measured. Blood glucose level greater than 250 mg/dL was considered diabetic.

This study divided rats into 1 day (short-term) and 4 consecutive weeks (long-terms) of daily administration. These groups were subdivided into four groups (n = 6 per group) each other for assessment of blood glucose level as follows: Group 1, untreated rats given distilled water; Group 2, untreated rats given *Opuntia ficus-indica*; Group 3, STZ-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*.

Analysis of food and water intake, body weight gain, and blood glucose

The food and water intakes of individual rats were measured daily. Body weight was evaluated each week. Blood was collected from the tail vein, and blood glucose was measured with a blood glucose monitoring device (GDoctor; Allmedicus Co., Korea). The experiments were conducted three weeks after the animal model was established.

Biochemical assays

At four weeks, the rats fasted for 12 hours before blood samples were collected. Blood was collected from the inferior vena cava of the animals and contained in SST Vacutainers (Becton Dickinson, USA). Plasma was centrifuged at 3,000 rpm for 15 minutes and then analyzed with a biochemical measuring instrument (HITACHI 7180; Japan) for albumin, alanine aminotransferase (ALT), aspartate transaminase (AST), cholesterol, creatinine, total protein, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and uric acid.

Statistical analysis

All statistics were carried out using IBM SPSS Statistic software version 22.0 (IBM Corp., USA). All analyses were replicated a minimum of three times. Data are expressed as mean \pm standard deviation, and comparisons among data were carried out using Student t-test or repeated measures ANOVA followed by Tukey's test. Mean values were considered to significantly differ at $p < 0.05$.

Results

Effects of *Opuntia ficus-indica* on body weight and food and water consumption

Table 1 shows body weight and food and water intake of the tested rats. A significant decrease in body weight was observed

Table 1. Body weight and food and water intakes of all experimental groups at 4 weeks

Parameter	Group 1	Group 2	Group 3	Group 4
Body weight (g)	336.83 ± 11.18	341.50 ± 13.11	224.50 ± 9.62*	288.17 ± 14.13*
Water intake (mL rat ⁻¹ day ⁻¹)	25.83 ± 3.69	29.90 ± 1.87	91.67 ± 16.36*	79.17 ± 13.99*
Food intake (g rat ⁻¹ day ⁻¹)	37.14 ± 0.45	44.19 ± 4.46	60.51 ± 6.60*	48.16 ± 6.76*

Values are presented as mean ± standard deviation.

Group 1, normal control given distilled water; Group 2, normal control given *Opuntia ficus-indica*; Group 3, streptozotocin (STZ)-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*.

* $p < 0.05$.

in STZ-induced diabetic rats and STZ-induced diabetic rats ingesting *Opuntia ficus-indica*. Food and water intake significantly increased in STZ-induced rats and STZ-induced diabetic rats ingesting *Opuntia ficus-indica* compared to untreated rats ($p < 0.05$). However, food intake significantly decreased in STZ-induced diabetic rats ingesting *Opuntia ficus-indica* compared to STZ diabetic rats ($p < 0.05$).

Effects of *Opuntia ficus-indica* on blood glucose in the rats with DM

Blood glucose level tests were conducted for experimental groups, and the results are presented in Fig. 1 and 2. Fig. 1 shows the level of blood glucose during the four weeks with/without *Opuntia ficus-indica*. STZ-induced diabetic rats had the highest blood glucose at two weeks. In particular, STZ-induced diabetic rats ingesting *Opuntia ficus-indica* had lower blood glucose at four weeks than at baseline. Fig. 2 shows the level of blood glucose during the one day after ingesting glucose with/without *Opuntia ficus-indica*. The group treated with *Opuntia ficus-indica* had a lower blood glucose level than the group treat with distilled water at 30 minutes. In addition, the group treated with *Opuntia ficus-indica* showed greater reduction in blood glucose with time. Blood glucose level in rats ingesting *Opuntia ficus-indica* significantly decreased ($p < 0.05$).

Assay of serum markers

The results of group analysis are presented in Table 2. This study analyzed albumin, AST, ALT, cholesterol, creatinine, total protein, triglyceride, HDL, LDL and uric acid levels. The levels of ALT, AST, and triglycerides were significantly reduced ($p < 0.05$).

Discussion

Drugs are very important in treating disease. However, drug treatments can cause side effects and are an annoyance as a daily preventive measure. Interest in the health benefits of foods this has increased to beyond the basic nutritional benefits to

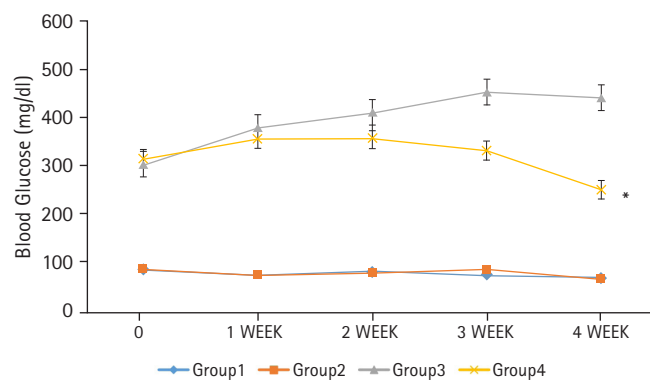


Fig. 1. Level of blood glucose in rats over four weeks. Values are expressed as mean ± standard deviation. Group 1, normal control given distilled water; Group 2, normal control given *Opuntia ficus-indica*; Group 3, streptozotocin (STZ)-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*. * $p < 0.05$.

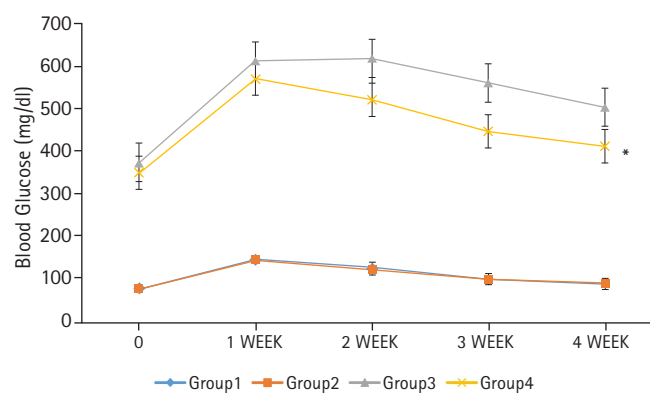


Fig. 2. Level of blood glucose in rats at 1 day. Values are expressed as mean ± standard deviation. Group 1, normal control given distilled water; Group 2, normal control given *Opuntia ficus-indica*; Group 3, streptozotocin (STZ)-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*. * $p < 0.05$.

disease prevention. Plant-derived agents are of interest as they may be less toxic and have fewer or weaker side effects than synthetic agents [13].

Table 2. Serum biochemical parameters at 4 weeks

	Group 1	Group 2	Group 3	Group 4
Albumin (g/dL)	2.92 ± 0.02	2.85 ± 0.17	2.33 ± 0.13	2.16 ± 0.03
ALT (U/L)	33.25 ± 1.55	34.25 ± 3.45	203.2 ± 27.33*	145.5 ± 31.65*
AST (U/L)	120.7 ± 21.0	135.90 ± 1.8	377.6 ± 59.11*	170.52 ± 47.21*
Cholesterol (mg/dL)	139.15 ± 1.05	108.50 ± 15.7	94.43 ± 7.25	113.5 ± 8.18
Creatinine (mg/dL)	0.51 ± 0.01	0.47 ± 0.04	0.58 ± 0.03	0.58 ± 0.06
Total protein (g/dL)	7.39 ± 0.06	6.71 ± 0.26	6.15 ± 0.06	5.83 ± 0.1
TG (mg/dL)	109.15 ± 0.65	105.2 ± 4.8	200.33 ± 110.86*	148.59 ± 21.32*
HDL (mg/dL)	41.01 ± 1.22	33.12 ± 2.89	37.65 ± 1.2	43.28 ± 3.04
LDL (mg/dL)	10.30 ± 0.56	8.36 ± 0.33	9.23 ± 1.1	11.94 ± 1.29
UA (mg/dL)	1.72 ± 0.14	1.58 ± 0.17	0.34 ± 0.01	0.87 ± 0.13

Values are presented as mean ± standard deviation.

Group 1, normal control given distilled water; Group 2, normal control given *Opuntia ficus-indica*; Group 3, streptozotocin (STZ)-induced diabetic rats given distilled water; Group 4, STZ-induced diabetic rats given *Opuntia ficus-indica*; ALT, alanine aminotransferase; AST, aspartate transaminase; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UA, uric acid.

* $p < 0.05$.

A recent study demonstrated growing concern about natural products and healthy foods, and research has increased regarding prevention and treatment of multiple diseases. The health benefits of various plants as well as the positive effects of their components have also been studied [14].

This study tested the effect of *Opuntia ficus-indica* on DM, as it has been reported to decrease blood glucose [10]. Several studies have demonstrated that *Opuntia ficus-indica* may be associated with treatment of several illnesses such as metabolic syndrome and renal, inflammatory, neoplastic, and neuronal diseases [15-18]. In particular, *Opuntia ficus-indica* has been shown to effectively treat DM through a significant decrease in serum glucose values after ingestion [5,19].

Opuntia ficus-indica prevented the diabetogenic effect of type 1 and 2 diabetic rats. This is possibly due to the presence of antioxidant compounds. Fat-soluble vitamins of cactus pear seed oil prevent diabetes in mice. Tocopherol has an antioxidant and anti-inflammatory activities and plasmatic antioxidant capacity and decreases LDLs [20]. *Opuntia ficus-indica* demonstrated antioxidant properties such as improved superoxide dismutase (SOD), reduced glutathione (GSH) and increased 2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging activity and exhibited free radical scavenging activity. In addition, AST, ALT, alkaline phosphatase (ALP), and malondialdehyde (MDA) were reduced, and hemoglobin, protein, and liver glycogen increased in diabetic rats after use. In particular, rich gallic acid in fruit reduces DNA damage and buffer free radical. In histopathological tests, pancreas tissue showed regeneration of beta cells upon treatment with *Opuntia ficus-indica* [20].

This study showed significant associations between *Opuntia ficus-indica* and ALT, AST, and triglycerides. Liver function

tests are commonly used in clinical practice to screen for liver disease and include serum aminotransferase, ALP, bilirubin, albumin, and prothrombin time. In particular, aminotransferases such as ALT and AST are key enzymes for liver function. Chronic mild elevation of transaminases is frequently found in diabetic patients [21-23]. *Opuntia ficus-indica* is associated with lipid metabolism, particularly decreased triglycerides [5]. This might be due to the role of the pectin in *Opuntia ficus-indica*. Pectin interferes with lipid absorption and reduces cholesterol [24,25]. The restoration of serum AST and ALT to their normal levels after administration of *Opuntia ficus-indica* may be due to revival of insulin secretion. This might be due to hepatoprotective effects of these antioxidants against hepatotoxic effect and may be due to the inactivation of cytosolic AST [20]. This study revealed that elevated levels of AST, ALT and triglycerides acid in diabetic rats were significantly reduced by *Opuntia ficus-indica*.

Our study did not conducted histopathological investigation. Because the histopathological examination by *Opuntia ficus-indica* have been observed in several reports. Histopathological examination of pancreatic β -cells showed regeneration of β -cells in group of rats that treated with *Opuntia ficus-indica* at repeated dose [20].

This study showed that *Opuntia ficus-indica* affected DM rats compared to controls. The researchers analyzed blood glucose level and the levels of several serum factors in DM rats and controls after feeding them *Opuntia ficus-indica*. Blood glucose level was measured at certain times after fasting, and serum blood level was measured after sacrifice.

The results of the present study indicate that *Opuntia ficus-indica* could reduce blood glucose and serum AST, ALT,

and triglycerides levels, indicating its potential as a treatment for DM. *Opuntia ficus-indica* might be a better alternative than drugs in managing DM in terms of cost and side effects. The limitations of this study are that the results were not tested for dose and/or time dependency, and only one animal species was tested. Further study of *Opuntia ficus-indica* is recommended in both animal and clinical studies. In addition, research using a larger sample size and longer experimental period is needed.

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