

RESEARCH ARTICLE

**EFFECT OF *CUCUMIS MELO* VAR. *FLEXUOSUS* LEAVES EXTRACT
ON RENAL OXIDATIVE INJURY AND INFLAMMATION IN
DIABETIC MALE ALBINO RATS**

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ABSTRACT

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Kidney disorders are common complications of uncontrolled diabetes. The present study aimed to evaluate the effect of oral administration of *Cucumis melo* var. *flexuosus* (snake melon or faqqous) leaves extract in three different doses (30, 60 and 120 mg/kg body weight) for 30 consecutive days on renal damage and inflammation in streptozotocin (STZ)-induced diabetic male albino rats (single intraperitoneal injection of 60 mg STZ/kg body weight). The results showed that the snake melon leaves extract induced a significant decrease in the plasma level of the kidney injury molecule-1 (KIM-1) in the diabetic rats. In addition, the snake melon leaves extract caused a significant decrease in the levels of the renal thiobarbituric acid reactive substances (TBARS), tumor necrosis factor alpha (TNF- α), interleukin (IL)-6, and caspase-3 of the diabetic rats. On the other hand, renal catalase (CAT) and superoxide dismutase (SOD) activities, as well as renal vascular endothelial growth factor (VEGF) level, were elevated significantly in the diabetic rats treated only with 60 mg or 120 mg of the snake melon leaves extract/kg body weight (compared with the diabetic control rats). In conclusion, the results of the present study revealed that the snake melon leaves extracts have a potential and effective role in inhibiting inflammation and oxidative stress in the kidney of diabetic rats.

INTRODUCTION

Diabetes mellitus, a metabolic disorder characterized by hyperglycemia with many other complications including microvascular and macrovascular complications, is one of the main causes of renal disorders^[1,2]. Oxidative stress, due to the overproduction of reactive oxygen species (ROS), in diabetic subjects is greatly involved in the pathogenesis of renal damage and dysfunction^[3,4]. Excessive production of free

radicals in diabetic rats caused renal damage through enhancing cellular lipid peroxidation, necrosis, and apoptosis^[5]. The traditional medicinal herbs act as exogenous antioxidants, which make a balance between oxidation and antioxidation in biological systems through inhibiting the propagation of oxidative chain reactions and serving as free radical and singlet oxygen scavengers at the cellular level^[6]. *Cucumis melo*, subsp. *melo* var. *flexuosus* (L.),

(family *Cucurbitaceae*) or snake melon (faqqous) is an ancient crop in many parts of the world. It used as a raw vegetable for salad, and in medicine as one of the natural antioxidants^[7]. It has many bioactive phytochemicals like alkaloids, flavonoids, tannins, and phenolic compounds that are responsible for its antioxidant property^[7,8]. Previously, the antihyperglycemic, insulin secretagogue, and neuroprotective activities of the snake melon leaves extract in streptozotocin (STZ)-diabetic rats were reported by our laboratory^[8,9]. The present study aimed to extend our laboratory findings by further exploring other beneficial effects of the snake melon through evaluating the renoprotective activity of three different doses of its leaves extract in STZ-induced diabetic male albino rats, with especial reference to the renal oxidative injury and inflammation.

MATERIAL AND METHODS

Extract

Snake melon leaves extract were collected from different healthy agricultural fields in Benha (Qalyubia, Egypt) and authenticated by our colleagues in the Faculty of Agriculture, Benha University. The fresh leaves were dried in dark area at room temperature, crushed to fine powder and extracted with ethanol using a Soxhlet apparatus as previously described^[8]. The extract was evaporated to dryness and stored at 4°C.

Experimental induction of diabetes

In the present study, diabetes was induced in experimental animals by a single intraperitoneal injection of 60 mg/kg body weight (b.wt) of freshly prepared solution of STZ (Sigma Co., St. Louis, MO, USA) dissolved in 0.1 M citrate buffer (pH 4.5) according to El-Shafey *et al.*^[10]. Rats were given 5% glucose solution in drinking water for two days to avoid hyperglycemic coma. Rats were examined for blood glucose levels 48 hours after STZ injection. Blood samples from the lateral tail vein of overnight fasted rats were withdrawn to measure glucose

concentration, and rats with glucose concentration ≥ 200 mg/dL were selected for the study.

Experimental design

Male Wistar albino rats (*Rattus norvegicus*), weighing 160 ± 10 g, were obtained from the Helwan Farm of Egyptian Organization for Vaccine and Biological Preparations. They were maintained under standard laboratory conditions (25 ± 2 °C, 12 hours light/dark cycle and given food and water *ad libitum*) for ten days before the onset of the experiment. Rats were humanely treated according to the ethical guidelines of the Faculty of Science, Benha University. They were randomly divided into five groups “seven rats each” as follows: (a) group I (non-diabetic control rats) that received vehicle (water) orally (by gavage) for 30 consecutive days, (b) group II (diabetic control rats) that injected intraperitoneally with a single dose of STZ (60 mg/kg b.wt) and housed under the same experimental conditions for 30 days, (c) groups III, IV, and V, STZ-diabetic rats that treated orally with 30, 60 or 120 mg/kg b.wt of snake melon leaves extract, respectively, dissolved in 1.0 mL distilled water for 30 consecutive days after inducing diabetes.

Sample preparations

At the end of the experiment, the overnight fasting animals were anaesthetized by light inhalation of diethyl ether; blood samples were drawn from the postcaval vein and directly transported to tubes containing ethylenediamine tetra-acetic acid (EDTA). Blood samples were centrifuged at $1500 \times g$ for 15 min; then plasma was separated and frozen at -20°C until used for kidney injury molecule-1 (KIM-1) analysis. The KIM-1 level was determined by a sandwich ELISA rat kit purchased from the Cloud-Clone Corporation (Katy, TX, USA). Immediately, kidneys were dissected out of the rats, washed, and homogenized in ice-cold phosphate buffer saline (PBS, pH 7.2). The homogenate was centrifuged at $5000 \times g$ for 5 min. The supernatants were stored at -20°C until used for the biochemical assays.

Biochemical assays in the kidney

The level of renal thiobarbituric acid reactive substances (TBARS) and the activities of catalase (CAT) and superoxide dismutase (SOD) were determined by colorimetric methods using kits purchased from BioVision (Milpitas, CA, USA). The concentrations of renal tumor necrosis factor (TNF- α), interleukin (IL)-6, vascular endothelial growth factor (VEGF), and caspase-3 were measured by ELISA rat kit purchased from the Cloud-Clone Corporation.

Statistical analysis

Results are presented as means \pm standard deviations of seven readings. Statistical analyses of the results were performed by the one-way analysis of variance (ANOVA), followed by Duncan's multiple range test^[11]. The significance level was set at $P < 0.05$ by using the Statistical Package for Social Science (SPSS) computer program (version 20.00) produced by IBM Software, Inc. Chicago, USA.

RESULTS

Effect of snake melon leaves extract on plasma KIM-1 level in STZ-diabetic rats

Figure "1" showed that the plasma KIM-1 level increased significantly ($P < 0.05$) in all diabetic groups compared with the non-diabetic group. On the other hand, the diabetic rats treated with snake melon leaves extract showed a significant decrease in the plasma KIM-1 level in a dose dependent-manner compared with the diabetic control rats.

Effect of snake melon leaves extract on renal oxidative stress parameters in STZ-diabetic rats

In the diabetic control rats, there was a significant increase ($P < 0.05$) in the renal TBARS level compared with all other groups (Table 1). The high dose of snake melon leaves extract (120 mg/kg b.wt) reduced the renal TBARS level of the diabetic rats more than the low and mild doses (30 and 60 mg/kg b.wt, respectively).

On the other hand, renal CAT and SOD activities reduced significantly ($P < 0.05$) in the diabetic control rats compared with the non-diabetic rats. While, the diabetic rats treated with snake melon leaves extract showed a significant increase in CAT and SOD activities, especially at the high doses (Table 1).

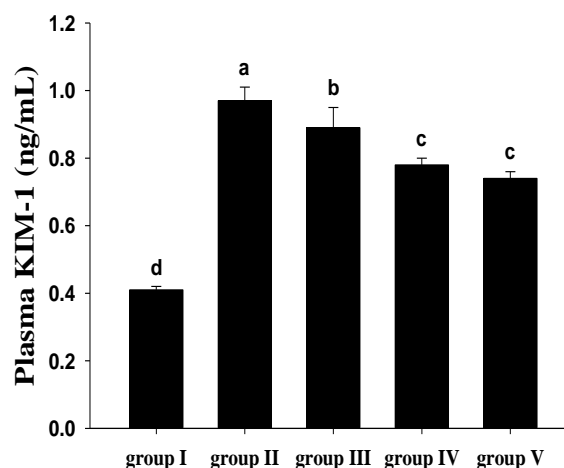


Figure 1: Effect of snake melon leaves extract on plasma kidney injury molecule (KIM)-1 level in streptozotocin (STZ)-diabetic rats. Data are presented as means \pm standard deviations ($n = 7$). Group I: non-diabetic control rats, group II: STZ-diabetic rats, groups III, IV, and V: STZ-diabetic rats received 30, 60 or 120 mg/kg body weight of snake melon leaves extract, respectively. Values with different letters in the figure were significantly different ($P < 0.05$).

Effect of snake melon leaves extract on renal proinflammatory cytokines in STZ-diabetic rats

The levels of proinflammatory cytokines (TNF- α and IL-6) elevated significantly ($P < 0.05$) in the renal tissues of diabetic control rats compared with the non-diabetic rats and the snake melon leaves extract treated diabetic rats (Table 2). While, the snake melon leaves extract induced a significant reduction in the renal pro-inflammatory cytokines levels of the diabetic rats.

Table 1: Effect of snake melon leaves extract on renal lipid peroxidation level and the activity of enzymic antioxidants in streptozotocin (STZ)-diabetic rats.

	Group I	Group II	Group III	Group IV	Group V
TBARS ($\mu\text{mol}/100 \text{ mg tissue}$)	12.25 \pm 1.96 ^d	25.37 \pm 1.79 ^a	22.31 \pm 0.83 ^b	20.12 \pm 0.53 ^b	17.53 \pm 0.69 ^c
CAT ($\mu\text{mol}/100 \text{ mg tissue}$)	1.33 \pm 0.10 ^a	0.62 \pm 0.04 ^d	0.67 \pm 0.10 ^{cd}	0.80 \pm 0.07 ^{bc}	0.88 \pm 0.06 ^b
SOD (U/100 mg tissue)	13.30 \pm 0.54 ^a	8.47 \pm 0.50 ^d	8.77 \pm 0.39 ^{cd}	9.57 \pm 0.41 ^{bc}	10.19 \pm 0.61 ^a

Data are presented as means \pm standard deviations ($n = 7$). Group I: non-diabetic control rats, group II: STZ-diabetic rats, groups III, IV, and V: STZ-diabetic rats received 30, 60 or 120 mg/kg body weight of snake melon leaves extract, respectively. TBARS: thiobarbituric acid reactive substances, CAT: catalase, SOD: superoxide dismutase. Values with different letters in the same row were significantly different ($P < 0.05$).

Table 2: Effect of snake melon leaves extract on renal proinflammatory cytokines (TNF- α and IL-6), VEGF, and caspase-3 levels in streptozotocin (STZ)-diabetic rats.

	Group I	Group II	Group III	Group IV	Group V
TNF- α (pg/100 mg tissue)	172.8 \pm 10.5 ^e	338.2 \pm 15.1 ^a	305.7 \pm 5.8 ^b	282.4 \pm 10.4 ^c	256.7 \pm 9.9 ^d
IL-6 (pg/100 mg tissue)	171.6 \pm 11.1 ^c	354.3 \pm 43.4 ^a	283.6 \pm 21.7 ^b	264.1 \pm 12.0 ^b	243.0 \pm 8.4 ^b
VEGF (pg/100 mg tissue)	369.3 \pm 37.0 ^a	224.2 \pm 27.2 ^d	260.4 \pm 8.5 ^{cd}	283.8 \pm 9.3 ^{bc}	321.3 \pm 19.1 ^b
Caspase-3 (ng/100 mg tissue)	4.45 \pm 0.64 ^d	10.11 \pm 0.97 ^a	8.89 \pm 0.14 ^b	7.62 \pm 0.38 ^c	7.14 \pm 0.13 ^c

Data are presented as means \pm standard deviations ($n = 7$). Group I: non-diabetic control rats, group II: STZ-diabetic rats, groups III, IV, and V: STZ-diabetic rats received 30, 60 or 120 mg/kg body weight of snake melon leaves extract, respectively. TNF: tumor necrosis factor, IL: interleukin, VEGF: vascular endothelial growth factor. Values with different letters in the same row were significantly different ($P < 0.05$).

Effect of snake melon leaves extract on renal vascular endothelial growth factor and caspase-3 levels in STZ-diabetic rats

Induction of diabetes in rats by STZ caused a significant decrease and increase ($P < 0.05$) in the renal VEGF and caspase-3 levels, respectively, compared with the non-

diabetic rats (Table 2). On the other hand, the renal VEGF level increased significantly, but the caspase-3 level reduced significantly, in the diabetic rats by the snake melon leaves extract especially at the higher doses (60 and 120 mg/kg b.wt, respectively).

DISCUSSION

Hyperglycemia enhanced ROS production in mesangial and tubular epithelial cells in diabetic rats, and hence increased the renal oxidative stress. It can also induce damage in the cells and micro-blood vessels of the kidney causing renal failure^[4,12]. In addition, oxidative stress has an essential role in the pathogenesis of acute and chronic kidney diseases^[13,14]. Induction of diabetes was carried out in the present study by using STZ, which increased the oxidative stress and augmented the destruction of beta cells in the Langerhans islets that are responsible for insulin secretion^[15]. The diabetic rats showed an elevation in the renal TBARS level and a reduction in the activities of renal enzymic antioxidant (CAT and SOD), probably due to the enhancement of free radical production by STZ. In addition, STZ-diabetic rat showed an elevation in the plasma KIM level. KIM-1, a transmembrane protein expressed in the damaged regions of proximal renal tubular epithelial cells, is considered as a sensitive biomarker for kidney injury^[16]. The elevation in the plasma KIM-1 level of the diabetic rats may also be attributed to the increment in the production of ROS and the reduction in the antioxidant defenses that induced by STZ^[17].

Many plant extracts and natural products of animal sources had both antioxidant and antidiabetic activities, which could protect kidneys from injury in diabetic subjects by improving the cellular antioxidant defense system and hence reducing the lipid peroxidation^[1,18,19]. Our previous study concluded that snake melon leaves extract showed a blood glucose lowering activity and improved the plasma insulin level in STZ-diabetic rats^[8]. In addition, the current study proved the renoprotective activity of snake melon leaves extract, which was able to decrease the plasma KIM-1 levels of diabetic rats, probably through its antioxidant effect. Indeed, snake melon leaves extract decreased the renal lipid peroxidation and improved the activities of CAT and SOD. Other research studies reported the free radical scavenging

activity of snake melon, which mainly related to its phenolic compounds especially flavonoids^[8,20].

The renal proinflammatory cytokines considered as biomarkers in the diagnosis of diabetic renal inflammation and injury, especially if the renal antioxidant defense system was weak^[21]. Excessive production of free radicals in the STZ-diabetic rats may activate many proinflammatory transcription factors and mediator leading to tissue inflammation and injury^[22]. Indeed, an increase in the renal proinflammatory cytokines (TNF- α and IL-6) was detected in the current study in the STZ-diabetic rats. Renal TNF- α may enhance cellular apoptosis, cause a disruption of the glomerular permeability barrier, and act as an inflammatory cofactor of high glucose level^[21,22]. On the other hand, snake melon extract reduced significantly the production of proinflammatory cytokines in renal tissues of STZ-diabetic rats, which likely resulted from its antioxidant and/or anti-inflammatory activities. Also, Preeti and Raju^[23] revealed that snake melon seeds had many bioactive components that showed many biological activities including the anti-inflammatory activity.

The VEGF, a protein secreted by podocytes of Bowman's capsule, is necessary for the survival of the endothelial cells, podocytes, and mesangial cells. Also, it is an essential regulator of angiogenesis and vascular permeability^[24]. Apoptosis is a natural mechanism of cell death that is regulated by cysteine-dependent specific aspartate proteases or caspases; activation of caspase-3 leads to an increase in apoptotic index^[21,25]. In the present study, STZ-diabetic rats showed a significant decrease and increase in the renal VEGF and caspase-3 levels, respectively. The reduction of VEGF expression was associated with podocyte loss and a defect in the glomerular filtration rate^[26]. In the current study, snake melon leaves extract (especially at the higher doses, 60 and 120 mg/kg b.wt) showed a renoprotective activity and succeeded to protect the

podocyte and decrease renal apoptosis in the diabetic rats by improving the renal VEGF level and decreasing the renal caspase-3, respectively.

In conclusion, the results of the present study revealed that the snake melon leaves extracts (especially at doses of 60 and 120 mg/kg b.wt) inhibited the renal damage of STZ-diabetic rats through: (a) improving the enzymic antioxidant defense system of renal tissues, (b) enhancing the production of renal VEGF, (c) decreasing the production of renal proinflammatory cytokines, (d) suppressing the renal lipid peroxidation and apoptosis.

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تأثير مستخلص أوراق نبات القثاء على الضرر الكلوي التأكسدي والالتهاب في ذكور الجرذان المُهَق المصابة بداء السكري

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قسم علم الحيوان، كلية العلوم، جامعة بنها، القليوبية، جمهورية مصر العربية

تُعتبر اعتلالات الكلى من المضاعفات الشائعة لداء السكري غير الخاضع للسيطرة الدوائية. ولذلك هدفت الدراسة الحالية إلى تقييم تأثير تناول اليومي لثلاث جرعات مختلفة (30، 60، 120 ملليجرام / كجم من وزن جسم الحيوان) من مستخلص أوراق نبات القثاء عن طريق الفم لمدة 30 يوم متتالية على الضرر والالتهاب الكلوي في ذكور الجرذان المُهَق المحدث بها داء السكري عن طريق الحقن داخل الصفاق بمادة الإستربتوزوتوسين (جرعة واحدة مقدارها 60 ملليجرام / كجم من وزن جسم الحيوان). وأظهرت النتائج أن مستخلص أوراق نبات القثاء أحدث انخفاضاً ذو دلالة إحصائية في مستوى جزيء الضرر الكلوي-I في بلازما دم الجرذان المصابة بداء السكري. كما أحدثت المعاملة بمستخلص أوراق نبات القثاء انخفاضاً ذو دلالة إحصائية في مستويات المواد التفاعلية التي تحتوي على حمض الثيوباربيتوريك، وعامل ألفا لنخر الورم، والإنترلوكين 6، وكاسباز 3 في أنسجة كلى الجرذان المصابة بداء السكري. وعلى الجانب الآخر ارتفع نشاط إنزيم الكاتاليز، ونشاط إنزيم السوبر أكسيد ديسميوتاز، وأيضاً مستوى عامل النمو البطاني الوعائي ارتفاعاً ذو دلالة إحصائية في أنسجة كلى الجرذان المصابة بداء السكري التي عوملت فقط بالجرعة 60 ملليجرام أو 120 ملليجرام من مستخلص أوراق نبات القثاء / كجم من وزن الجسم (مقارنة بمجموعة الجرذان المحدث بها داء السكري ولم تعامل بمستخلص أوراق نبات القثاء). وخلصت هذه الدراسة إلى أن مستخلص أوراق نبات القثاء له دور فعال في تثبيط الالتهاب والضرر التأكسدي في كلى الجرذان المصابة بداء السكري.