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ORIGINAL ARTICLE

Neuroprotective effect of *Cucumis melo* Var. *flexuosus* leaf extract on the brains of rats with streptozotocin-induced diabetes

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Abstract The central nervous system is one of the most vulnerable organs affected by the oxidative stress associated with diabetes mellitus. Healthy food provides an important source for antioxidants. Therefore, the protective effect of *Cucumis melo* var. *flexuosus* (*C. melo* var. *flexuosus*) leaf extract on the brains of diabetic rats was investigated. Adult male albino rats divided into 5 groups of 6 rats each were assigned into a normal control group and four diabetic groups. Diabetes was induced in rats by a single intraperitoneal injection of streptozotocin (STZ; 60 mg/kg bw). One of the four diabetic groups was left untreated and was considered as a diabetic control group while the three other groups were treated with *C. melo* var. *flexuosus* leaf extract at the doses of 30, 60 and 120 mg/kg bw for a period of 30 days. After completion of experimental duration plasma and brains were used for evaluating biochemical changes. The obtained data showed that *C. melo* var. *flexuosus* leaf extract treatment lowered blood glucose, glycated hemoglobin, brain tumor necrosis factor-alpha, interleukin levels, brain malondialdehyde content and caspase-3 activity. Furthermore, the treatment resulted in a marked increase in plasma dopamine, melatonin, brain vascular endothelial growth factor-A levels, brain catalase and superoxide dismutase activities. From the present study, it can be concluded that the *C. melo* var. *flexuosus* leaf extract exerts a neuroprotective effect against oxidative damage associated with diabetes.

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Keywords Diabetic neuropathy · *Cucumis melo* Var. Flexuosus · Hypoglycemia · Proinflammatory cytokines · Oxidative stress · Apoptosis

Introduction

The balance between the production of reactive oxygen species (ROS) and the antioxidant defense systems is critical for maintaining a healthy biological system (Ajarem et al. 2015). The overproduction of ROS and the reduction of antioxidant defense systems lead to oxidative stress, which plays an important role in the development and progression of diabetes and its complications (Ceretta et al. 2012). This oxidative stress associated with diabetes affects several cell functions, metabolism, and gene expression, which in turn can cause various tissues damage (Sireesha and Rao 2015). The brain is the most vulnerable tissue to oxidative damage as a result of its high oxygen consumption rate, abundant lipid content and low levels of enzymatic and non-enzymatic antioxidants (Abdel Moneim 2015).

Recently accumulated evidence has shown that natural antioxidants can prevent and treat the onset of diseases caused by overproduction of ROS (Ajarem et al. 2015). *Cucumis melo* var. *flexuosus* (*C. melo* var. *flexuosus*) is one of the ancient horticultural crops in many parts in the world, including Middle East, Asia, northern Africa (Abdel-Ghani and Mahadeen 2014). It appears in Egyptian mural paintings among the vegetables listed in the bible as being eaten by the Hebrews in Egypt (Paris 2012). It is known as agoor (Mariod et al. 2009), Armenian cucumber, snake cucumber, snake melon (Soltani et al. 2010) and faqqous (Janick et al. 2007). The fruit is usually slender, almost three feet long and three inches in diameter, and is almost always bent and twisted (Soltani et al. 2010), rind light green to green-striped, ribbed

or wrinkled, flesh white, non-sweet, usually monoecious and eaten immature as cucumbers or pickled (Nesom 2011). *C. melo* var. *flexuosus* is a very popular salad plant, which contains some amounts of carbohydrates, minerals, and vitamins (Mariod et al. 2009). In diabetes phytotherapy, the effects of *C. melo* var. *flexuosus* leaf had never been demonstrated experimentally in either clinical or experimental diabetes up until now. Therefore, the present study was aimed to evaluate the possible neuroprotective effect of *C. melo* var. *flexuosus* leaf in brains of streptozotocin (STZ)-induced diabetic rats.

Materials and methods

Plant material

Leaves of *C. melo* var. *flexuosus* were collected in Augustus 2015 from Benha, Egypt. The plant was identified by Dr. Mahran El Nagar (Department of Horticulture, Faculty of Agriculture, Benha University, Benha, Egypt).

Extract preparation

The leaves of *C. melo* var. *flexuosus* were cleaned, dried in the shadow and crushed in a grinder to give 3 g of leaves powder. Powdered leaves were extracted with 70 % ethanol using a Soxhlet apparatus. The solvent was evaporated under reduced pressure in rotary vacuum at 35–40 °C. Finally, the extract was weighed (yield: 10 %), stored at −10 °C, and used to treat the animals as needed. Freshly prepared suspension of the extract was further diluted with distilled water to obtain different doses.

Acute toxicity study

The mean lethal dose (LD50) of the aqueous ethanolic extract of *C. melo* var. *flexuosus* leaf was determined in rats using the method described by Lorke 1983.

Animals

Thirty male Wistar albino rats weighing 120–140 g were obtained from Helwan Farm of Egyptian Organization for Vaccine and Biological Preparations, Egypt. All animals were housed under standard conditions (22 ± 1 °C, 12 h light/12 h dark cycle) with food and water ad libitum and were acclimated to the laboratory conditions for 7 days prior to starting the experiment.

Induction of diabetes mellitus

Diabetes was induced in overnight fasted rats by a single intraperitoneal injection of a freshly prepared solution of STZ (60 mg/kg bw, 0.01 M citrate buffer, pH 4.5; Sigma-Aldrich). Three days after injection, rats with fasting blood glucose levels above 200 mg/dL were scored as diabetic and included in the experiment.

Experimental design

Rats were divided randomly into five groups (n = 6 rats/group): normal control (NC), diabetic control (DC), diabetic treated with *C. melo* var. *flexuosus* leaf extract (30 mg/kg bw orally) (D + CMF30), diabetic treated with *C. melo* var. *flexuosus* leaf extract (60 mg/kg bw orally) (D + CMF60), and diabetic treated with *C. melo* var. *flexuosus* leaf extract (120 mg/kg bw orally) (D + CMF120). The treatment was started on the fourth day after STZ injection and this was considered as the first day of treatment.

Blood and tissue sampling

After 30 days from the treatment, overnight fasting animals were sacrificed under ether anesthesia. The blood samples were collected from a post caval vein and directly transported to tubes containing EDTA (El-Gomhorya Co., Egypt). A portion of these blood samples were separated by centrifugation at 1500 xg for 15 min. Then, the supernatants were stored as plasma at −20 °C.until assayed. The other portion of blood samples was used for glycated hemoglobin estimation. Brains were immediately removed and then were washed and homogenized in ice-cold phosphate buffer saline (PBS) (pH 7.2). After centrifugation at 5000 xg for 5 min, the clear supernatant was stored at −20 °C to be used for biochemical analysis.

Determination of blood glucose and glycated hemoglobin

Blood glucose level was estimated according to the method of Burtis and Ashwood (2006), while glycated hemoglobin (HbA1c) was estimated using Glycohemoglobin Reagent Set from Pointe Scientific Inc. (USA).

Determination of plasma dopamine and melatonin

Plasma dopamine and melatonin levels were assayed by rat dopamine ELISA kit purchased from Uscn Life Science Inc. (USA) and rat melatonin ELISA kit purchased from Kamiya Biomedical Company (USA).

Determination of oxidative stress markers

Homogenates of the brain were used for the determination of malondialdehyde (MDA) content according to Brindeiro et al. (2012), catalase (CAT) activity as described by Aebi (1984) and superoxide dismutase activity (SOD) according to Nishikimi et al. (1972).

Determination of proinflammatory cytokines

Tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 levels were measured in the brain homogenates by rat ELISA kits purchased from Uscn Life Science Inc. (USA) and the Cloud-Clone Corporation (USA), respectively.

Determination of caspase-3 activity and vascular endothelial growth factor-a

Caspase (CASP)-3 activity and vascular endothelial growth factor (VEGF)-A level were measured in the brain homogenates by rat ELISA kits purchased from the Cloud-Clone Corporation (USA).

Statistical analysis

All results were expressed as the mean ± SD. Data for multiple variable comparisons were analyzed by one-way analysis of variance (ANOVA). For the comparison of significance between groups, Duncan's test was used as a post hoc test according to the Statistical Package for the Social Sciences (SPSS version 20.00). Experimental differences were considered statistically significant if $P < 0.05$.

Results

Acute toxicity

Acute toxicity studies revealed the non-toxic nature of *C. melo* var. *flexuosus* leaf extract as the treated rats appeared normal and did not display any significant changes in behavior or neurological responses up to 480 mg/kg body weight of the extract. There was no mortality or toxicity reaction at any of the doses until the end of the study.

Effect of *C. melo* Var. *flexuosus* leaf extract on blood glucose and glycated hemoglobin

As shown in Table 1, the blood glucose and glycated hemoglobin levels of DC, D + CMF30, D + CMF60 and D + CMF120 groups were significantly increased ($p < 0.05$) as compared to NC group. The administration of *C. melo* var. *flexuosus* leaf extract to STZ-induced diabetic rats in groups D + CMF30, D + CMF60 and D + CMF120 significantly reduced the blood glucose and glycated hemoglobin levels as compared to the DC group. The blood glucose and glycated hemoglobin lowering effects of *C. melo* var. *flexuosus* leaf extract were in a dose-dependent manner.

Effect of *C. melo* Var. *flexuosus* leaf extract on plasma dopamine and melatonin

Table 2 reveals a significant decrease ($p < 0.05$) in plasma dopamine and melatonin levels in DC, D + CMF30, D + CMF60 and D + CMF120 groups as compared to NC group. While, diabetic rats treated with *C. melo* var. *flexuosus* leaf extract (30, 60 and 120 mg/kg) showed significantly increased plasma dopamine and melatonin levels dose dependently.

Effect of *C. melo* Var. *flexuosus* leaf extract on oxidative stress markers

The MDA levels were greatly increased ($p < 0.05$) in brains of DC, D + CMF30, D + CMF60 and D + CMF120 groups as compared to those of NC group. The treatment of diabetic rats with *C. melo* var. *flexuosus* leaf extract (30, 60 and 120 mg/kg) decreased the elevated MDA levels in brains of diabetic rats in a dose dependent pattern. On the other hand, the activities of antioxidant enzymes (CAT and SOD) were decreased in brains of DC, D + CMF30, D + CMF60 and D + CMF120 groups as compared to those of NC group. The activities of antioxidant enzymes in the brain of diabetic rats treated with three different doses of *C. melo* var. *flexuosus* leaf extract were dose-dependently elevated as compared to those of DC group (Table 3).

Effect of *C. melo* Var. *flexuosus* leaf extract on proinflammatory cytokines

The levels of TNF-α and IL-6 were significantly increased ($p < 0.05$) in brains of DC, D + CMF30, D + CMF60 and D + CMF120 groups as compared to NC group. Elevated TNF-α and IL-6 levels in brains of diabetic rats were reduced with the treatment *C. melo* var. *flexuosus* leaf extract (30, 60 and 120 mg/kg) in a dose dependent pattern (Table 4).

Table 1 Effect of *C. melo* var. *flexuosus* leaf extract on blood glucose and glycated hemoglobin levels in diabetic rats.

Groups parameters	NC	DC	D + CMF30	D + CMF60	D + CMF120
Glucose (mg/dl)	123.96 ± 0.27^{e}	348.16 ± 2.02^{a}	295.17 ± 1.39^{b}	238.25 ± 2.22^{c}	162.76 ± 2.16^{d}
HbA_{1c} (%)	4.50 ± 0.14^{e}	7.17 ± 0.12^{a}	6.80 ± 0.10^{b}	6.20 ± 0.11^{c}	5.40 ± 0.10^{d}

Data are expressed as means ± SD ($n = 6$)

Values within a row not sharing a common letter differ significantly at $P < 0.05$

Table 2 Effect of *C. melo* var. *flexuosus* leaf extract on plasma dopamine and melatonin levels in diabetic rats

Groups parameters	NC	DC	D + CMF30	D + CMF60	D + CMF120
Dopamine (pg/ml)	475.41 ± 7.71^{a}	302.53 ± 6.79^{e}	346.68 ± 5.40^{d}	385.28 ± 4.49^{c}	413.39 ± 1.98^{b}
Melatonin (pg/ml)	461.84 ± 2.42^{a}	319.32 ± 7.84^{e}	349.04 ± 3.89^{d}	385.54 ± 3.55^{c}	394.73 ± 4.39^{b}

Data are expressed as means ± SD ($n = 6$)

Values within a row not sharing a common letter differ significantly at $P < 0.05$

Effect of *C. melo* Var. *flexuosus* leaf extract on caspase-3 activity and VEGF-A

As shown in Table 5, the activities of caspase-3 increased while, the VEGF-A levels decreased significantly ($p < 0.05$) in brains of DC, D + CMF30, D + CMF60 and D + CMF120 groups as compared to those of NC group. However, *C. melo* var. *flexuosus* leaf extract (30, 60 and 120 mg/kg) treatment reduced the activities of caspase-3 and elevated the VEGF-A levels in brains of diabetic rats. *C. melo* var. *flexuosus* leaf extract showed a maximum effect at a dose of 120 mg/kg.

Discussion

Diabetes mellitus is the most common metabolic disorder that is characterized by chronic hyperglycemia resulting from defective insulin secretion, resistance to insulin action or both (Ibrahim and Abd El-Maksoud 2015). STZ-induced hyperglycemia is a widely used to induce experimental diabetes in animals (El Shafey et al. 2013; Hassan et al. 2015). In the present study, the blood glucose and glycated hemoglobin levels increased after STZ injection. On the other hand, *C. melo* var. *flexuosus* leaf extract treatment significantly reduced the blood glucose and glycated hemoglobin levels in the diabetic groups. These results indicate the hypoglycemic effect of *C. melo* var. *flexuosus* leaf extract in diabetic rats.

Dopamine is an endogenous catecholamine that was first recognised as a neurotransmitter in the central nervous system (Cools et al. 2011). Outside the nervous system, dopamine has several different functions in the body. Garcia Barrado et al. (2015) reported that dopamine is involved in the survival of rat pancreatic beta cells and modulates the insulin release through the dopamine D2 receptors (Shankar et al. 2006). Moreover, dopamine agonist treatment ameliorates hyperglycemia, hyperlipidemia, and the elevated basal insulin release from islets of ob/ob mice (Liang et al. 1998).

It was demonstrated that diabetes decreases the plasma dopamine level. Azevedo et al. (1983) suggested that plasma dopamine activity would be reduced in cases of diabetic neuropathy due to the destruction of sympathetic nerve endings. Moreover, hyperglycemia during diabetes is reported to damage dopaminergic function (Shankar et al. 2007). However, treatment of diabetic rats with *C. melo* var. *flexuosus* leaf extract increased the plasma dopamine levels in a dose-dependent manner.

Melatonin is a neurohormone secreted from pineal gland (Gürpınar et al. 2012). It possesses powerful antioxidant properties and is capable of scavenging oxygenous and nitrogenous free radicals (Peschke et al. 2015). Several studies suggested that melatonin had also a neuroprotective effect because it modulates neuroinflammation by inhibiting the NF-κB pathway and downstream mediators of inflammation, and protects against oxidative stress (Espino et al. 2001; Agil et al. 2013). Furthermore, melatonin administration in early stages of diabetes could improve hyperglycemia, polyphagia and polydipsia in rats (Bibak et al. 2014).

It was observed that there was a marked reduction in plasma melatonin level in diabetic rats that may be due to increased utilization for scavenging free radicals. On the other hand, treatment of diabetic rats with *C. melo* var. *flexuosus* leaf extract increased the plasma melatonin, which may be due to the low level of ROS.

In the present study, increased levels of lipid peroxidation (represented by increased MDA) in brains of diabetic rats were observed and that may be due to hyperglycemia. Hfaiedh et al. (2013) reported that hyperglycemia led to the overproduction of free radicals, which in turn cause lipid

Table 3 Effect of *C. melo* var. *flexuosus* leaf extract on oxidative stress markers in brains of diabetic rats

Groups parameters	NC	DC	D + CMF30	D + CMF60	D + CMF120
MDA (nmol/mg protein)	1.10 ± 0.04^{e}	3.16 ± 0.03^{a}	2.76 ± 0.06^{b}	2.59 ± 0.02^{c}	2.24 ± 0.03^{d}
CAT (μmol/mg protein)	2.61 ± 0.06^{a}	1.16 ± 0.02^{e}	1.48 ± 0.03^{d}	1.73 ± 0.02^{c}	1.96 ± 0.02^{b}
SOD (U/mg protein)	10.98 ± 0.09^{a}	6.58 ± 0.10^{e}	7.66 ± 0.04^{d}	8.81 ± 0.03^{c}	9.14 ± 0.02^{b}

Data are expressed as means ± SD ($n = 6$)

Values within a row not sharing a common letter differ significantly at $P < 0.05$

Table 4 Effect of *C. melo* var. *flexuosus* leaf extract on proinflammatory cytokines in brains of diabetic rats

Groups parameters	NC	DC	D + CMF30	D + CMF60	D + CMF120
TNF-α (pg/mg protein)	122.03 ± 1.84^{e}	223.73 ± 4.01^{a}	198.56 ± 1.67^{b}	183.57 ± 0.53^{c}	161.41 ± 0.99^{d}
IL-6 (pg/mg protein)	214.88 ± 2.90^{e}	384.81 ± 4.78^{a}	342.42 ± 0.93^{b}	315.79 ± 1.06^{c}	292.15 ± 2.93^{d}

Data are expressed as means ± SD (n = 6)

Values within a row not sharing a common letter differ significantly at $P < 0.05$

peroxidation and membrane damage leading to impaired neuronal activity in diabetes mellitus (Shaikh and Shrivastava 2014). Several studies have suggested that an overproduction of ROS may be the major factor impairing sensory nerves and dorsal root ganglia (Zangiabadi et al. 2011) and may also contribute to the neuromuscular and metabolic deficits in diabetic neuropathy (Espino et al. 2001). While the reduction in antioxidant enzymes activities might be due to their increased utilization to scavenge free radicals. This is in agreement with the findings of Cemek et al. (2008) and da Costa et al. (2013). Treatment with *C. melo* var. *flexuosus* leaf extract has increased the activities of antioxidant enzymes, which could be a result of decreased lipid peroxidation production. Mandana et al. (2012) reported that seed oil of *C. melo* var. *flexuosus* contains essential fatty acids including linoleic acid and linolenic acid. The essential fatty acids have a positive correlation with antioxidant activity (Kirmizigul et al. 2007) while linolenic acid has been reported to play an important role in neuroprotection as well as exhibiting anti-inflammatory and neoplastic properties (Piermartiri et al. 2015). Moreover, Mariod et al. (2009) reported that seed oil of *C. melo* var. *flexuosus* had a medium amount of tocopherols when compared with other common oils such as sesame oil, groundnut oil, or sunflower oil and these tocopherols may be important in the protection against oxidative stress.

The nervous system in diabetes undergoes a proinflammation process that leads to developing the neuropathy symptoms (Liu et al. 2012). In the present study, a marked increase in the release of proinflammatory cytokines (TNF-α and IL-6) was observed in brains of diabetic rats and that may be due to hyperglycemia. In support to this view, Sandireddy et al. (2014) reported that hyperglycemia activated numerous metabolic pathways like polyol pathway, protein kinase c pathway, advanced glycation end products pathway, and the hexosamine pathway. All these pathways could directly or indirectly initiate and progress the neuroinflammation and nerve damage leading to the neuropathic pain. Shi et al. (2013) also reported that hyperglycemia-induced inflammation affects the structural features of a neuron as the glycosylation of myelin protein. Proinflammatory cytokines also damage myelin sheath and increases nerve excitability, thus leading to edema and neuroinflammation (Tiwari et al. 2011).

Treatment with *C. melo* var. *flexuosus* leaf extract significantly inhibited the increased of proinflammatory cytokines in brains of diabetic rats, thus blocking the inflammatory pathways involved in the progression of diabetic neuropathy. The anti-inflammatory effect of *C. melo* var. *flexuosus* leaf extract might be due to decreasing blood glucose and ROS levels in diabetic rats treated with *C. melo* var. *flexuosus* leaf extract. It also may be due to increasing the plasma melatonin level in diabetic rats treated with *C. melo* var. *flexuosus* leaf extract. In support to this view, Kahya et al. (2015) reported that melatonin and selenium reduce plasma cytokine and brain oxidative stress levels in diabetic rats.

Hyperglycemia could seriously contribute to mitochondrial dysfunction such as the release of cytochrome C, activation of caspase-3, altered biogenesis and fission, which all lead to a programmed cell death (Hosseini and Abdollahi 2013). Caspase-3 is regarded as an indicator of apoptosis (Mao et al. 2014). The present investigation showed the remarkable elevation of caspase-3 activity in diabetic rat brain and this effect was blocked by *C. melo* var. *flexuosus* leaf extract treatment, indicating that *C. melo* var. *flexuosus* leaf extract decreased neuronal death in diabetic rat brain.

VEGF-A is a member of the cysteine knot family of growth factors, which is best known for its essential roles in blood vessel growth (Medinger and Passweg 2014). However,

Table 5 Effect of *C. melo* var. *flexuosus* leaf extract on caspase-3 activity and vascular endothelial growth factor-A level in brains of diabetic rats

Groups parameters	NC	DC	D + CMF30	D + CMF60	D + CMF120
CASP-3 (ng/mg protein)	3.47 ± 0.06^{e}	6.87 ± 0.05^{a}	6.16 ± 0.04^{b}	5.67 ± 0.03^{c}	5.15 ± 0.03^{d}
VEGF-A (Pg/mg protein)	470.44 ± 2.22^{a}	258.09 ± 2.68^{e}	294.59 ± 3.46^{d}	321.39 ± 1.71^{c}	348.45 ± 1.73^{b}

Data are expressed as means ± SD (n = 6)

Values within a row not sharing a common letter differ significantly at $P < 0.05$

evidence has emerged that VEGF-A also promotes a wide range of neuronal functions, including neurogenesis, neuronal migration, neuronal survival and axon guidance (Mackenzie and Ruhrberg 2012). Furthermore, VEGF-A protected brain endothelial cells against hypoglycemia by enhancing glucose passage, reducing endothelial cell death, and ameliorating paraendocellular permeability (Zhao et al. 2015). The present investigation showed the remarkable elevation of caspase-3 activity in diabetic rat brain and this effect was blocked by *C. melo* var. *flexuosus* leaf extract treatment, indicating that *C. melo* var. *flexuosus* leaf extract decreased neuronal death in a diabetic the rat brain.

In conclusion, the findings of the present investigation suggest that *C. melo* var. *flexuosus* leaf extract has beneficial effects on diabetic oxidative stress, inflammation, and apoptosis in rat brains may be attributed to its hypoglycemic and antioxidant activities. However, Future studies are needed to investigate regarding clinical applications.

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