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Research Article

ANTIHYPERGLYCEMIC, ANTIOXIDANT, AND PANCREAS PROTECTIVE EFFECTS OF *Coriandrum sativum* SEED IN ALLOXAN-INDUCED DIABETIC RATS

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ABSTRACT

Coriandrum sativum is a medicinal plant, used in traditional medicine for diabetes therapy. The goal of the this study was to determine the antidiabetic, antioxidant and pancreas protection effects of ethanol extracts of *C. sativum* seeds (CSE) in alloxan-induced diabetic rats. The male Wistar rats were induced diabetic by intraperitoneal injection of alloxan (150mg/kg BW). CSE was prepared and administrated orally to the animals at the dose of 125 and 250mg/kg for 28 days. Blood glucose level was measured, and antioxidant status was assessed by determining the activities of superoxide dismutase, glutathione peroxidase as well as malonyl aldehyde in liver. Histopathological study of pancreas was conducted at the end of experimental period. Both dose of CSE showed the glucose lowering effect, corrected antioxidant status of diabetic animals in liver and protected the pancreas organ from damage.

Key words: *Coriandrum sativum seed*, antihyperglycemia, antioxidant, pancreas protection

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by the increasing of blood glucose level due to reduction of insulin secretion and or performance. Type 2 DM is caused by decreasing of insulin secretion or insulin receptor sensitivity that is typically occurred in people who are obese or overweight due to their lifestyle. Oral antidiabetic drugs that are widely used include sulfonylureas, biguanides, tiazolidindion and glinide. The side effects and expense of these drugs often leads to patient non-compliance in the administration of medications that can cause uncontrolled blood glucose levels lead to complications (Piero *et al.*, 2012).

Uncontrolled hyperglycemia causes an increased production of oxygen free radicals through autoxidation of glucose and non-enzymatic glycation of proteins, resulting the increase of oxidative stress, which contributes to the reduction of insulin action and insulin excretion. The levels of main enzymes that regulate the antioxidant defenses, such as Superoxide dismutase (SOD), Glutathion Peroxidase (GSH-Px) and Catalase, are affected by diabetes (Rajeshwari and Andallu, 2011; Vega-Monroy and Fernandez-Mejia, 2013). Appropriate support for enhancing antioxidant supplies may help to prevent clinical complications of diabetes mellitus (Rahbani-Nobar, 1999).

In Indonesia *Coriandrum sativum* seed is not only used as flavoring agent, but also empirically used as traditional medicine for treatment of diabetes. *C. sativum* seed was reported to possess antihyperglycemic as well as antioxidant properties. The increased dietary intake of *C. sativum* seeds decreases the oxidative stress in DM (Deepa and Anuradha, 2010). To establish pharmacology effects in diabetes mellitus, the present study evaluated the antidiabetic, antioxidant and pancreas protective effects of *C. sativum* seed in alloxan-induced diabetic rats.

MATERIAL AND METHODS

C. sativum seeds, ethanol, alloxan, normal saline E, CMC Na 1% solution, EDTA, protease inhibitor, reagens for SOD and GPx assay (xanthine, xanthine oxidase, Bovine Serum Albumin (BSA), diethylenetriamine-pentaacetic acid, nitroblue tetrazolium (NBT), sodium carbonate, diNa-bathocuproine-disulphonic acid salt, $CuCl_2$, glutathione, glutathione reductase, NADPH, H_2O_2.

Preparation of extract

The air dried powdered of *C. sativum* seeds (500g) was extracted with ethanol by maseration methods for 24h. Ethanol extract was evaporated under pressure to obtain dry extract.

Animal

Wistar albino rats (150-200g) were maintained in room temperature, were maintained in given standart pellet diet and water ad libitum during the experiment period. The extract and standart drug were given orally.

Antihyperglycemic activity test

The animals were fasted for 16h prior to the induction of diabetes. Aloxan monohydrate (dissolved in 0.9% NaCl) was administered i.p. at a single dose of 150mg/kg (Tripathi and Chandra, 2009). Four days after diabetes induction, rats with blood glucose level of 200mg/dl or higher were considered to be diabetic and selected for the experiment. Diabetic animals were randomly assigned to groups. Group I contained normal animals and served as normal control. Group II served as diabetic control (toxic). Groups I and II received vehicle (CMC Na 1%) during the experiments, while Group III and IV received the extract dose of 125 mg/kg BW and 250mg/kg BW respectively. The treatment was conducted for 4 weeks. Serum glucose level was measured every week. At the end of the treatment, animals were sacrificed. The liver was removed and used for antioxidant assay, while the pancreas was used for histopathology test.

Antioxidant assays

SOD activity was measured by Sun *et al.* method (1989) with modification. Liver supernatant (0.06mL) was reacted with the mixture of 2.70mL sodium carbonate buffer 50mM containing 0.1mM EDTA (pH 10), 0.06mL xantin 10mM, 0.03mL BSA 0.5%, and 0.03mL *nitroblue tetrazolium* (NBT) 2.5mM. Xanthine oxidase 0.04 Unit was added. The absorbance of assay mixture was measured after 30min at 560nm. PBS containing 11.5g/L KCl was used as control solution. SOD activity (%) was calculated using formula: 1-(A/B) x 100%, where A: sample absorbance and B: control solution absorbance.

GPx activity was determined by Lawrence and Burk (1976) with modification. Two hundred µL of liver supernatant was reacted with 200µL of phosphate buffer 0.1M pH 7.0 containing EDTA 0.1mM, 200µL of reduced glutathion (GSH) 10 mM and 200µL of glutathion reductase (2.4 unit). The mixture was incubated for 10 minutes at 37°C, 200µL of NADPH 1.5mM was added and incubation was continued for 3min at the same temperature, followed by addition of 200µL H_2O_2 1.5mM. The absorbance was measured at 340nm. GPx activity was calculated by the formula:

M unit GPx = (A x Vt x 2 x 1000 x 1/mg protein) / 6.22 x Vs

where A: absorbance, Vt: total volume (mL), Vs: sample volume (mL)

MDA activity assay was conducted by Singh *et al.* (2002), with modification. One mL of liver supernatant was reacted with 4mL of mixture of cold HCl 0,25 N containing 15% TCA, 0.38% TBA, 0.5% BHT). The mixture was heated at 80°C for 1h, cooled and centrifuged at 3500rpm for 10min. The absorbance of supernatant was measured at 532nm, using tetraoxypropane (TEP) as standart reference.

Histopathology study

The whole pancreas from each animal was removed after sacrificing the animal under anesthesia and was collected in 10% formalin solution and immediately processed by the paraffin technique. Sections of 5µm thickness were cut and stained by hematoxylin and eosin (H and E) for histological examination (Tatar *et al.*, 2012)..

Statistical analysis

All data are presented as means ± S.D. for six rats in each group. Comparisons between groups and between time points were made by one-way analysis of variance (ANOVA) followed by t-test to analyze the difference. Differences were considered significant when p values were less than 0.05.

Table I. Effect of CSE on blood glucose level in alloxan-induced diabetic rats

Group	Blood glucose level (mg/dL)±SD					
	Day 0	Day 4	Day 11	Day 18	Day 25	Day 32
I	79.64±3.33	80.16±3.66*	80.84±3.79*	81.65±3.27*	82.33±3.39*	83.40±3.98*
II	75.50±1.69	242.80±2.76	243.44±3.09	245.62±3.40	246.62±2.69	248.05±2.59
III	73.51±3.23	239.56±10.81	216.89±3.58*	206.61±6.77*	182.26±4.81*	159.21.±2.62*
IV	74.86±3.22	243.26±3.23	214.93±5.81*	187.97±2.05*	160.92±3.76*	130.26±3.52*

*: significantly different to diabetic control (P<0.05)
I : Normal control; II : Diabetic control; III : CSE125mg/kg BW; IV : CSE 250mg/kg BW

Table II. Effect of CSE on antioxidant activity

Group	SOD (%)	GPx (U/mg)	MDA (nmol/mg)
I	87.54 ± 0.72*	36.27 ± 0.11*	4.05 ± 0.45*
II	16.72 ± 1.93	8.57 ± 0.22	14.80 ± 0.39
III	35.49 ± 0.49*	12.69 ± 0.16*	8.54 ± 0.38*
IV	84.47 ± 0.72*	29.94 ± 0.33*	4.55 ± 0.13*

*: significantly different to diabetic control (P<0.05)
I : Normal control; II : Diabetic control; III : CSE 125 mg/kg BW; IV : CSE 250mg/kg BW

RESULTS AND DISSCUSION

Antihyperglycemic activity

The antidiabetic effects of *C. sativum* seed extract (CSE) on diabetic rats are shown in Tables I. Intraperitonial injection of alloxan produced increasing of blood glucose level up to above of 24 mg/dL on 4th day, indicated diabetic condition. Treatment of the CSE (125 as well as 250mg/kg) in alloxan-induced diabetic rats resulted in a significant decrease in the elevated blood glucose levels.

Gray and Flatt, (1999), have demonstrated the insulin release and insulin like activity of *C. sativum* in streptozocin-diabetic mice. Deepa and Anuradha (2011) reported the significant decrease of blood glucose level after treatment with *C. sativum* seeds powder, increase in plasma insulin level as well as reduction in glycated haemoglobin as compared to untreated diabetic rats.

Antioxidant activity

Effect of daily administration of CSE for 4 weeks on antioxidant activity was showed on tabel II. Hyperglycemia induced glucose auto-oxidation, protein glycation and subsequent oxidative degradation of glycated proteins leading to increase in ROS formation, which potentially damage the biomolecules. SOD and GPx activity were significantly decreased on alloxan-induced diabetic group, while MDA activity as significantly increased, associated with lipid peroxidation. Elevated levels of lipid peroxidation in plasma and tissue is one of the characteristic profil of chronic diabetes and hence inhibition of free radical generation and oxidative damage could be considered as an important strategy in management of diabetes mellitus (Deepa and Anuradha, 2011).

Significantly increasing of SOD and GPx activity, as well as decreasing of MDA indicated the potent antioxidant activity of CSE. This activity was correlated to the constituent of the seed such as linalool, limoene, quercetin, rutin, sitosterol, cineole, p-hydroxy benzoic acid and many other compunds including tannins (Deepa and Anuradha, 2011).

Pancreas histopathology study

Histopathology of normal pancreas (Figure 1-I) showed normal appearance and size of the Islet of Langerhans located in the exocrine tissues. Pancreas of diabetic control rat (1-II), showed marker degeneration of the Islet of Langerhans. The diameter of the cells were decreased and the nucleous were unclear, indicated the cell necrotic.

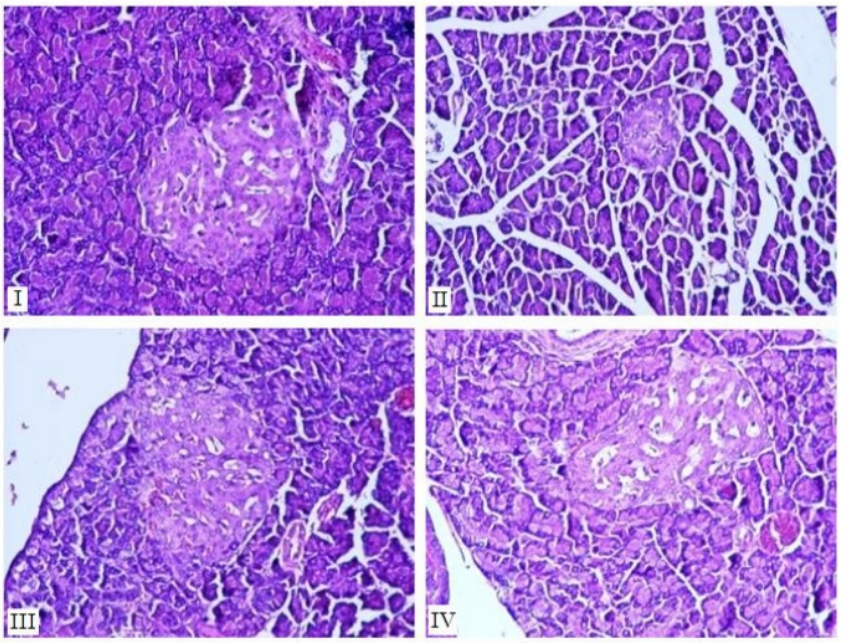

Figure 1. Histopathology of the pancreas (I:normal control, II:diabetic control, III: CSE 125mg/kg BW, IV: CSE 250mg/kg BW)

Alloxan has been found to be selectively toxic to pancreatic beta cells due to it accumulation in the beta cells as glucose analogues. Cytotoxic action of alloxan is mediated mainly by the generation of reactive oxygen species (ROS). Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals, which undergo dismutation to hydrogen peroxide (H_2O_2) followed by formation more highly reactive hydroxyl radicals. Then the cytosolic calcium concentration significantly increases, causes rapid destruction of beta cells of pancreatic islets (Rohilla and Ali, 2012).

The morphology and size of the Islet of Langerhans of SCE-treated (125 mg as well as 250 mg/kg BW) pancreas (figure 1-III&IV) revealed remarkable improvement than those of diabetic control group (figure 1-II). Antioxidant properties of SCE facilitated to enriched the antioxidant content, which could prevent the lipid peroxidation and protect against toxic effect of free radicals. H_2O_2-induced oxidative stress could be supressed by polyphenolic compounds from *C. sativum* seeds.

CONCLUSION

C. sativum seeds extract dose of 125mg/kg BW and 250mg/kg BW showed antihyperglycemic effect, enhanced antioxidant activity, as well as protected pancreas organ from damage on alloxan-induced diabetic rat. Further studies are needed to investigate and elucidate the mechanism of action of active compound of SCE.

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