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Full Length Research Paper

Blood glucose levels and pathology of organs in alloxan-induced diabetic rats treated with hydro-ethanol extracts of *Allium sativum* and *Capparis spinosa*

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Diabetes mellitus (DM) is a growing health concern worldwide. Use of plants for treatment of DM is widely practiced in the Middle East. Garlic (*Allium sativum L.*) and *Capparis spinosa* are traditionally used as antidiabetic medications. The present study evaluated the differential effects of ethanol extraction of these plants on the blood glucose concentration and the pathology of pancreatic β-cell mass, liver, lungs, kidneys and GI tract in diabetic rats. DM was induced in 30 out of 40 adult female Albino rats, using intraperitoneal injection of 120 mg/kg BW alloxan. The diabetic rats were assigned into three groups, two of which were treated with extract of garlic and *C. spinosa* fruits (300 mg/kg) for 12 days and the rats of the third group, as the untreated group received ordinary diet. Ten non diabetic rats remained as the normal control group. Administration of these extracts tended to decrease the blood glucose concentration, while the blood glucose of the untreated rats remained significantly high. The garlic extract was found to be more effective than *C. spinosa* extract. Histopathologically, tissue sections of the pancreas in the treated rats did not show a significant difference with the untreated diabetic rats. The liver of the treated diabetic rats with garlic extract revealed slight improvement in the hepatic tissue compared to those of the untreated diabetic rats. This study indicated a significant anti-hyperglycemic effect of garlic and *C. spinosa* fruit and supported its traditional usage in treatment of diabetes mellitus.

Key words: Diabetes mellitus, garlic, *capparis spinosa,* histopatological changes, pancreatic islets.

INTRODUCTION

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas and/or by the ineffectiveness of the insulin produced. It takes two major forms; type 1 and type 2 diabetes mellitus. Although the two types of diabetes have distinct pathogenesis, hyperglycemia and insulin resistance, various hyperglycemia-related complications are the most common features in both forms (Rajagopal and Sasikala, 2008; Eddouks et al., 2005). Increase in sedentary lifestyle, consumption of energy-rich diets and obesity are some of the factors resulting in the rise in the number of diabetics (Eidi et al., 2006). Diabetes is recognized as one of the leading causes of morbidity and mortality in the world. While about 2.5 to 7% of the world's population has been diagnosed with diabetes mellitus, it is still expected to increase in future (Abo et al., 2008).

In spite of the fact that synthetic drugs such as insulin are the most important therapeutic agents known to medicine, researchers have been making efforts to find insulin-like substances from plant sources for the treatment of diabetes (Rafiq et al., 2009). More than 1200 plant species have been recommended for the treatment

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of diabetes (Jouad et al., 2000; Eddouks et al., 2003). Recent scientific investigation and clinical studies have confirmed the efficacy of some medicinal plants and herbal preparations in the improvement of normal glucose homeostasis. Herbal therapy have been used in patients with insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic peripheral neuropathy and other consequences of this metabolic disease (Mukherjee et al., 2006). The herbal drugs are prescribed widely because of their effectiveness, fewer side effects and relatively low cost (Venkatesh et al., 2003).

Plants may act on blood glucose through different mechanisms including facilitating insulin's activity, acting as potential insulin-like substances, inhibiting insulinase activity and increasing the quality and/or quantity of the β-cells in the pancreas by enhancing regeneration of these cells. The fiber of plants may also interfere with carbohydrate absorption; thus affecting blood glucose (Shanmugasundaram et al., 1990; Nelson et al., 1991; Jelodar et al., 2005).

Garlic (*Allium sativum L.*) is a common spicy flavoring agent used since ancient times. Garlic has been cultivated in all over Iran for its characteristic flavor, foodstuff, condiment and medicinal properties (Eidi et al., 2006). In the past decade, some protective effects of garlic have been well established by epidemiological studies and animal experiments. Commercially available garlic preparations in the form of garlic oil, garlic powder and pills are widely used for certain therapeutic purposes, including lowering blood pressure and improving lipid profile (Elkayam et al., 2003). Other pharmacological effects of garlic have mostly been attributed to its hypoglycemic, anticoagulant, antibiotic, hypocholesterolaemic, antihepatotoxic, anticancer, immune system modulatory and antioxidant properties (Augusti and Sheela, 1996; Bordia et al., 1996; Yoshida et al., 1998; Ali et al., 2000; Amagase et al., 2001; Bakri and Douglas, 2005).

Capparis spinosa (*C. spinosa*) is a plant belonging to Capparidaceae family. *C. spinosa* is one such plant established to have highly diverse economic and medicinal value in different system of medicines like in Iranian, Greece, Chinese, and Greco-Arabi System of medicines (Azaizeh et al., 2003).

C. spinosa is used in phytomedicine around the world as anti-oxidative, antifungal, antihepatotoxic, anti-inflammatory and anti-diabetic (Al-Said et al., 1988; Ali-Shtayeh and Abu Ghdeib, 1999; Gadgoli and Mishra, 1999; German et al., 2002; Azaizeh et al., 2003).

Furthermore, it has been reported that some species of the genus *Capparis* possess chondroprotective effect, antiallergic potency and hypolipidemic effects (Eddouks et al., 2005; Panico et al., 2005; Trombetta et al., 2005). The methanol extract of *C. spinosa* showed a noteworthy antioxidant/free radical scavenging effectiveness in various *in vitro* models and this extract has been suggested to treat oxidative stress-based pathological diseases (Bonina et al., 2002; German et al., 2002).

However, many researchers demonstrated that garlic possesses a variety of medicinal properties such as hypoglycaemic activity. To our knowledge, there are a few documents about the medicinal properties and side effects of *C. spinosa* in the treatment of diabetes mellitus. Therefore, the objective of this study was to examine the influence of the oral administration of *C. spinosa* extract on the blood glucose concentration in comparison with garlic extract and to evaluate histopathological changes in pancreas, liver, kidneys, heart, lungs, stomach, large and small intestines and spleen of the alloxan-induced diabetic rats.

MATERIALS AND METHODS

Animals

The experiments were performed in adult female albino rats weighing 200 to 220 g. The animals were housed under standard environmental conditions (23±1°C, with 55±5% humidity and a 12 h light/dark cycle) and maintained with free access to water and *ad libitum* standard laboratory diet (70% carbohydrates, 25% proteins, 5% lipids). The rats were randomly assigned into three diabetic and one control groups (n = 10). The study was approved by the local ethics committee of our faculty, in accordance with the ethics standards of "Principles of Laboratory Animal Care".

Induction of diabetes

Diabetes was induced in 30 rats by single intraperitoneal injection of 120 mg/kg BW of alloxan tetrahydrate (10%) (Sigma, St. Luis, MO, USA). The rats were fasted for 12 h before and after injection of alloxan. The range of the diabetogenic dose of alloxan is quite narrow and even light overdosing may be toxic and result in loss of many animals (Szkudelski, 2001). This dose was selected according to the previous studies (Mansour et al., 2002; Sheweita et al., 2002). Each rat of the normal control group was injected with the same amount of normal saline. The rats with blood glucose above 250 mg/dl, as well as with polydipsia and polyurea, which last for at least 3 days, were selected for the experiment.

Preparation of the garlic and *C. spinosa* fruit extracts

Fresh garlic bulbs (*A. sativum L.*) and *C. spinosa* fruit were purchased from a retail food store (Shiraz, Iran) in March 2011. The plants were identified by Dr Karachi, Department of Pharmacology and samples were deposited at the herbarium, Shiraz University. For preparation of garlic extract, the dried and ground bulbs (approximately 100 g) were submitted for extraction with 300 ml ethanol (80%) in a Soxhlet apparatus for 72 h. After extraction, the solvent was filtered and then evaporated by Rotavapor®. The obtained garlic alcoholic extract was then stored at -20°C until being used. Extract of the *C. spinosa* was prepared according to the same method.

Experimental design

In the present experiment, 40 rats (30 diabetic, 10 normal) were used. The rats were divided into four groups. Ten rats were used in

Table 1. Effect of *Allium sativum* and *Capparis spinosa* on blood glucose (mg/dl) during the 12 days of treatment.

Group	Day 1 to 4	Day 5 to 8	Day 9 to 12	Day 1 to 12
Control	95.20±0.95^{a}	95.15±0.92^{a}	95.00±1.30^{a}	95.12±0.59^{a}
diabetic	569.25±18.26^{c}	545.19±22.07^{c}	585.25±17.06^{c}	565.23±11.41^{c}
C. spinosa	341.00±34.95^{b}	346.50±33.30^{b}	377.89±45.20^{b}	352.40±21.13^{b}
Garlic	303.33±41.44^{b}	255.88±39.05^{b}	276.83±49.33^{b}	278.85±24.43^{b}
P-value	0.00	0.00	0.00	0.00

Means within a column with different superscript letters (a, b, c) denote significant differences. *P<0.05* was accepted as statistically significant.

each group.

Group 1: Normal control rats were administrated 1 ml normal saline.
Group 2: Diabetic (positive) control rats were administrated 1 ml normal saline.
Group 3: Diabetic rats were administrated garlic alcoholic extract (1 ml/kg BW, equivalent to 300 mg/kg) daily using an intragastric tube for 12 days.
Group 4: Diabetic rats were administrated *C. spinosa* alcoholic extract (1 ml/kg BW, equivalent to 300 mg/kg) daily using an intragastric tube for 12 days.

Blood glucose measurement

Blood glucose was measured every day until the end of experiment. Blood was collected from the tail of the animals after 12 h fasting. The tail was embedded in alcohol and about one millimeter of its end was cut and a drop of blood was used for the blood glucose test with the help of a glucometer; Easy Gluco (Ames, Korea) and further sampling did not need re-cutting of the tail. Accuracy of the glucometer was checked by the Orthotolidin method.

Histopathological evaluation

Fifteen days after diabetes induction and at the end of the 12 days treatment, the animals of all groups were euthanized by Xylazin (5 mg/Kg) and Ketamin HCl (40 mg/kg).

Appropriate tissue samples were collected from pancreas, liver, kidneys, heart, lungs, stomach, large and small intestines and spleen and were then fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 μm thicknesses, and stained with hematoxylin-eosin for light microscopic examination.

Statistical analysis

Descriptive statistics including the mean, standard error, median, minimum and maximum were calculated for all variables. The one-way ANOVA followed by Turkey post hoc test were used for comparison of different parameters. The data were analyzed by SPSS software, version 16 and P<0.05 was accepted as statistically significant.

RESULTS

Effect of garlic and *C. spinosa* extracts on the blood glucose

The effects of oral administration of the garlic and *C. spinosa* extracts on the blood glucose in the diabetic rats have been shown in Table 1. The blood glucose concentration in the untreated diabetic rats was significantly higher at all intervals after intraperitoneal administration of alloxan in comparison to those of the normal rats (*P<0.05*). While the glucose concentration of the untreated rats remained high at all intervals, administration of garlic and *C. spinosa* extract at doses of 300 mg/kg body weight tended to bring the blood glucose significantly toward normal values from day 2 onwards. The garlic extract was found to be more effective than *C. spinosa* extract. The normal rats did not exhibit any significant alterations in their blood glucose concentration during the course of the study.

Histopathological findings

In the untreated diabetic rats, alloxan resulted in severe necrotic changes of the pancreatic islets, particularly the cells in the center of the islets. Nuclear changes such as pyknosis, karorrhexis, karyolysis; disappearance of nucleus and in some places, residues of the destroyed cells were visible. Relative reduction in the size and number of the islets especially those around the central vessel together with severe reduction in the β- cells were demonstrated in these animals (Figure 1). Histopathological study of the treated diabetic rats that received garlic and *C. spinosa* extracts did not show a significant difference with the untreated diabetic rats (Figure 2). The cellular integrity and architecture of pancreases were intact in the control group.

The histopathologic sections of the liver of the untreated diabetic rats showed degenerative changes in the hepatocytes represented by disorganization of the hepatic cords, congestion of the central veins with mild hepatocellular necrosis and the sinusoids were infiltrated by mild nonspecific inflammatory cells. The hepatocytes of the untreated rats showed morphological change such as pyknosis, karyorrehexis, chromatolysis and cytoplasmic vacuolization (Figure 3). However, the liver of the treated diabetic rats with garlic extract revealed slight improvement in the structure of the hepatic tissue compared to those of the untreated diabetic ones, except for a few mildly degenerated hepatocytes around the

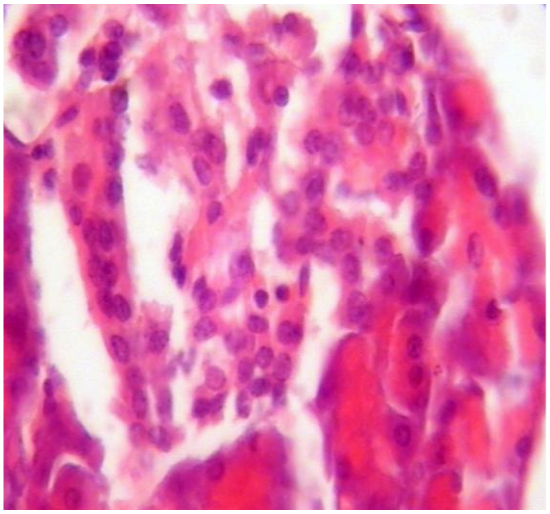

Figure 1. The pancreas section from an untreated diabetic rat.

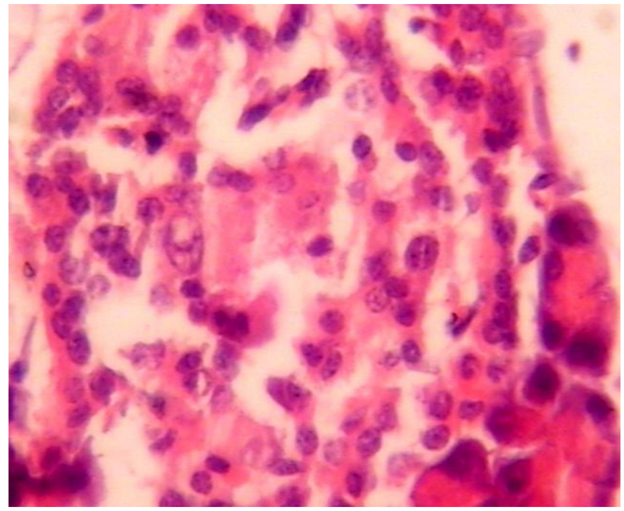

Figure 2. Pancreas section from a treated diabetic rat.

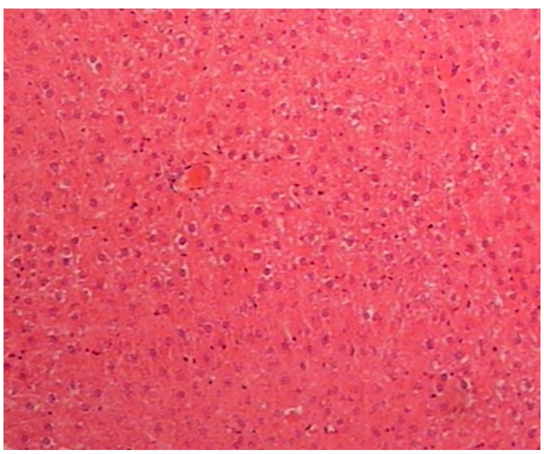

Figure 3. Liver section from an untreated diabetic rat.

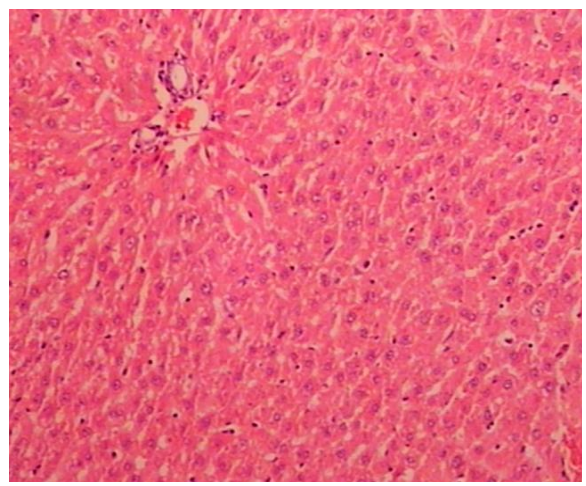

Figure 4. Liver section from a treated diabetic rat.

central vein of the garlic treated rats which still had some cytoplasmic vacuoles, other hepatocytes and portal and sinusoidal areas were almost normal (Figure 4). There was no evidence of regeneration in the liver of diabetic rats that received the *C. spinosa* extract. The liver of the normal control rats had normal structure.

The kidneys of the normal control rats had normal structure and the proximal and distal convoluted tubules, renal corpuscles, glomerulus and glomerular capsule had normal architecture. Microscopic examination of the kidneys of the treated and untreated diabetic rats showed mild tubular necrosis with moderate degenerative and necrotic changes in the glomerular epithelium and diffused interstitial and glomerular hemorrhages.

No lesions was found in the heart, lungs, stomach, large and small intestines and spleen of either normal controls, treated or untreated diabetic rats.

DISCUSSION

Diabetes mellitus is the most common endocrine disorder that affects more than 285 million people worldwide. The number is expected to grow to 438 million by 2030, corresponding to 7.8% of the adult population. In addition to the primary effects of diabetes, this disease is accompanied by increased risk factors such as hyperglycemia, hypertension, dyslipidemia, decreased fibrinolytic activity, severe atherosclerosis and increased platelet aggregation (Williams and Pickup, 2004; Rajalakshmi et al., 2009).

Despite the remarkable development in the treatment of diabetes mellitus by synthetic drugs, side effects such as hypoglycemia at higher dose administration, low oral bioavailability due to degradation in stomach, inactivation and digestion by proteolytic enzymes in the luminal cavity, and poor permeability across the intestinal epithelium, make it necessary to find other alternatives (Mohini et al., 2012; Mukherjee et al., 2006). Therefore, there is much interest in discovering natural treatments without negative side effects that can reduce these risk factors in diabetic patients.

Although many investigators reported that garlic possesses a variety of medicinal properties such as hypoglycaemic and hypolipidaemic activities, to our knowledge, there are a few documents about medicinal properties and side effects of *C. spinosa* in the treatment of diabetes mellitus. The results of the present study showed that daily oral administration of 300 mg/kg ethanol extract of garlic and *C. spinosa* for 12 days decreased the blood glucose concentrations into normal range in the alloxan-induced diabetic rats. Therefore, the present study reinforces the findings of previous papers that garlic had a significant effect in reducing blood glucose (Sheela et al., 1995; Jelodar et al., 2005; Liu et al., 2005; Eidi et al., 2006).

However, several hypotheses have been proposed by researchers, it is not yet clear how garlic actually works in reducing blood glucose in diabetes mellitus. The hypoglycemic action of garlic could possibly be due to an increase in pancreatic secretion of insulin from β-cells, release of bound insulin or enhancement of insulin sensitivity (Thomson et al., 2007). Augusti and Sheela (1996) stated that the antioxidant effect of S-allyl cysteine sulfoxide, an isolated product from garlic, may contribute to its beneficial effect in diabetes. Further, it has also been suggested that these disulphide compounds have the effect of sparing insulin from –SH inactivation by reacting with endogenous thiol-containing molecule such as cysteine, glutathione, and serum albumins (Jain and Vyas, 1975). Another mechanism recommended by Jain and Vyas (1975) states that garlic may act as an antidiabetic agent by increasing either the pancreatic secretion of insulin from the β-cells or it influences on release of bound insulin.

In agreement with our results, Eddouks and colleagues (2004) stated that the aqueous extracts of *C. spinosa* fruits exerted a significant and potent anti-hyperglycaemic activity in STZ-diabetic rats. Lemhadri et al. (2007) demonstrated that repeated oral administration of the aqueous *C. spinosa* extract for two weeks was accompanied by an important improvement in glucose tolerance and a strong decrease of body weight in highly glucose intolerant HFD mice.

The mechanism underlying the reported therapeutic activity may involve, at least, an improvement of insulin sensitivity which can lead to an increase in peripheral glucose utilization (Bavenholm et al., 2001). Another possible action site for *C. spinosa* to exert its postprandial hypoglycemic effect is in the gastrointestinal tract. These plants may slow the digestion of food and decrease the rate of carbohydrate absorption and clearing the postprandial glucose load (Eddouks et al., 2004). In the experiment carried out by Eddouks et al. (2004), the extract of *C. spinosa* fruits had no effect on basal plasma insulin concentrations in both normal and diabetic rats. It appears that the fruit extracts of this plant is responsible for a hypoglycaemic effect independently of insulin secretion. Therefore the hypoglycaemic activity of this plant may be due to inhibition of hepatic glucose production and/or stimulation of glucose utilization by peripheral tissues, especially muscle and adipose tissues. C. spinosa extract could also act as inhibitors of tubular renal glucose re-absorption (Eddouks et al., 2003).

Compounds such as flavonoids, alkaloids, lipids and glucosinolates are the main constituents of *C. spinosa* (Brevard et al., 1992; Sharaf et al., 2000). Their even-tual hypoglycaemic effect in type 1 diabetes mellitus has not been established. However their potential effect on antihepatotoxic and anti-inflammatory activities has been shown (Al-Said et al., 1988; Gadgoli and Mishra, 1999).

Histopathological study of diabetic untreated rats revealed degeneration of pancreatic islet cells, which was due to alloxan used in this experiment. However, signs of regeneration of β-cells have been reported following consumption of some plant extracts (Shanmugasundaram et al., 1990; Ayber et al., 2001; Suba et al., 2004; Yadev et al., 2008).

Pancreas of the diabetic treated rats did not show a significant difference with the diabetic rats. This finding reveals that the hypoglycemic effects of garlic and *C. spinosa* are not through the action of these plants on the number of β-cells and this will support the theory that hypoglycemic effect of garlic and *C. spinosa* might be due to the action of substances like S-methylcysteine sulfoxide and flavonoids or due to an increase in the insulin response (Eddouks et al., 2004; Jelodar et al., 2005).

Conclusion

In conclusion, the present study demonstrated that repeated oral administration of garlic and *C. spinosa* extracts for 12 days evokes a beneficial effect on the hyperglycaemia in the diabetic rats. However, the garlic extract was found to be more effective than *C. spinosa* extract, the pancreas of the treated rats did not show an improvement in their histological architecture. These results support the traditional usage of the garlic and *C. spinosa* extracts in treatment of diabetes mellitus.

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